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21

CONTENTS

JANUARY

EDITORIALS: I. Airways revisited 1
R. S. Vaughan

II. Anaesthesia of the skin.......... 4
S. Coley

ORIGINAL ARTICLES

Defining a standard intubating position using "Angle Finder"...................................... 6
W. A. Horton, L. Fahy and P. Charters

Awake fibreoptic intubation in the patient at high risk of aspiration 13
A. Ovassapian, T. C. Krejcie, S. J. Yelich and M. H. M. Dykes

In vivo assessment of percutaneous local anaesthetic preparations.................................. 17
D. F. McCafferty, A. D. Woolfson and V. Boston

Studies on morphine disposition: influence of general anaesthesia on plasma concentrations of morphine and its metabolites 22
J. W. Sear, C. W. Hand, R. A. Moore and H. J. McQuay

Studies on morphine disposition: influence of renal failure on the kinetics of morphine and its metabolites.. 28
J. W. Sear, C. W. Hand, R. A. Moore and H. J. McQuay

Effect of halothane, enflurane and isoflurane on carotid body chemoreceptor activity in the rabbit and the cat.................................... 33
J. Ponte and C. L. Sadler

Effect of thiopentone, etomidate and propofol on carotid body chemoreceptor activity in the rabbit and the cat.................................... 41
J. Ponte and C. L. Sadler

Computer controlled infusion of propofol.......... 46
R. M. Tackley, G. T. R. Lewis, C. Prys-Roberts, R. W. Boaden, J. Dixon and J. T. Harvey

Propofol for induction and maintenance of anaesthesia: comparison between younger and older patients 54
G. L. Scheepstra, L. H. D. J. Booij, C. L G. Rutten and L. G. J. Coenen

Early cortical auditory evoked response in anaesthesia: comparison of the effect of nitrous oxide and isoflurane 61
D. E. F. Newton, C. Thornton, P. Creagh-Barry and C. J. Doré

Adrenal cortical reserve in patients undergoing muscle biopsy for malignant hyperthermia screening.................... 66
M. J. Fairbrass, P. Coe and F. R. Ellis

Oxygen consumption and carbon dioxide elimination in infants and children during anaesthesia and surgery 70
S. G. E. Lindahl

Glycopyrronium requirements for antagonism of the muscarinic side effects of edrophonium 77
P. Dodd, S. J. Day, D. R. Goldhill, D. M. MacLeod, P. S. Withington and P. M. Yate

Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy.............. .. 82
B. Drenger, Y. Shir, D. Pode, A. Shapiro, F. Magora and J. T. Davidson

Does pretreatment with cimetidine and ranitidine affect the disposition of bupivacaine? 87
R. J. Flynn, J. Moore, P. S. Collier and E. McClean

RAPID COMMUNICATION

Median nerve evoked potentials during propofol anaesthesia.................................... 92
G. L. Scheepstra, J. J. de Lange, L. H. D. J. Booij and H. H. Ros

CASE REPORTS

Use of continuous prolonged administration of atracurium in the ITU to a patient with myasthenia gravis.................................. 95
B. J. Pollard, N. J. N. Harper and B. R. H. Doran

A new therapeutic approach to accidental intra-arterial injection of thiopentone.. 98
M. Vangerven, G. Delrue, E. Brugman and P. Cosaert

Neurogenic pulmonary oedema precipitated by induction of anaesthesia 101
N. Braude and T. Ludgrove

Fatal haemopathological consequences of general anaesthesia....................... 104
P. J. Wright, J. R. Shortland, J. D. Stevens, M. A. Parsons and J. Watkins

Acute gastric dilatation in an incarcerated hiatus hernia............... 108
C. S. Hopkins and S. Leith

CORRESPONDENCE

Hypotensive agents: an animal model............. 112
Spinal anaesthesia with bupivacaine.... 112
Teaching fibreoptic intubation.................... 113

Use of propofol in a patient with porphyria 114
Spinal anaesthesia and surgical blood loss 114

BOOK REVIEWS

Annual Review of Pulmonary and Critical Care Medicine 88/89 116
Intensive Care—Pocket Reference 116
Principles of Airway Management 116
Introduction to Anesthesia: The Principles of Safe Practice 116
Diamorphine: Its Chemistry, Pharmacology and Clinical Use 117
Care of the Critically Ill 117
Medicine for Disasters 117
Anaesthesia Review 5 118
Recent Advances in Critical Care Medicine 118

FEBRUARY

EDITORIAL · Cisapride and anaesthesia 121
D. J. Rowbotham

ORIGINAL ARTICLES

Effects on the lower oesophageal sphincter of cisapride given before the combined administration of atropine and neostigmine 124
M. J. Jones, R. W. D. Mitchell and N. Hindocha

Effects of general anaesthesia with halothane on antroduodenal motility, pH and gastric emptying rate in man 129
B. A. Schurizek, L. H. O. Willacy, K. Kraglund, F. Andreasen and B. Juhl

Comparison of 1.5% enflurane with 1.25% isoflurane in oxygen for Caesarean section: avoidance of awareness without nitrous oxide 138
M. E. Tunstall and A. Sheikh

Preliminary evaluation of the Enclosed Magill Breathing System 144
W. E. Bruce and N. C. Soni

Comparison of the Bain and the ADE system during controlled ventilation in adults 150
N. K. Shah, C. J. Loughlin and R. F. Bedford

Comparison of the Magill and Lack anaesthetic breathing systems in anaesthetized patients 153
S. W. Millar, P. K. Barnes, N. Soni and R. Tennant

Effect of oral doxapram on morphine-induced changes in the ventilatory response to carbon dioxide 159
N. P. C. Randall, B. J. Pleuvry, E. J. Fazackerley, C. Y. Modla, L. F. Prescott and T. E. J. Healy

Plain bupivacaine: 0.5% or 0.25% for spinal analgesia? 164
T. H. Nielsen, E. Kristoffersen, K. H. Olsen, H. V. Larsen, H. C. Husegaard and M. Wernberg

Relationship between alveolar deadspace and arterial oxygenation in children with congenital cardiac disease 168
R. Fletcher

Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis 177
C. J. R. Parker and J. M. Hunter

Is vecuronium a long-acting neuromuscular blocking agent in neonates and infants? 184
O. A. Meretoja

Effect of surface electrode positioning on the compound action potential evoked by ulnar nerve stimulation in anaesthetized infants and children 188
I. Kalli

Haemodynamic effects of vecuronium 194
J. M. K. H. Wierda, E. Maestrone, A. F. Bencini, A. Boyer, O. M. Rashkovsky, H. Lip, R. Karliczek, J. M. Ket and S. Agoston

Changes in oxygen saturation during inhalation induction of anaesthesia in children 199
M. M. Sampaio, P. M. Crean, S. R. Keilty and G. W. Black

RAPID COMMUNICATIONS

Effect of diluting propofol on the incidence of pain on injection and venous sequelae 202
D. N. Stokes, N. Robson and P. Hutton

Comparison of continuous paravertebral and extradural infusions of bupivacaine for pain relief after thoracotomy 204
P. J. Matthews and V. Govenden

CASE REPORTS

Oxygen desaturation following sedation for regional analgesia 206
D. C. Smith and J. F. Crul

Pancuronium allergy: a case report 210
G. Patriarca, E. Nucera, D. Schiavino, A. Romano, V. Di Rienzo, S. Pellegrino and G. Fais

Heart block following propofol: a case report 213
M. F. M. James, C. J. Reyneke and K. Whiffler

Profound intraoperative atelectasis 216
S. I. Samuels and J. B. Brodsky

ABSTRACTS

Proceedings of the Anaesthetic Research Society, London Meeting, November 11, 1988 .... 219P

CORRESPONDENCE

Neuromuscular block in diaphragm and hand 236
Nasotracheal intubation, paranasal sinusitis and head injuries 236

Prolonged suxamethonium-induced neuromuscular block associated with organophosphate poisoning 237
Measurement of transdiaphragmatic pressure 237

BOOK REVIEWS

Intravenous Anaesthesia 239
Positioning the Surgical Patient 239

MARCH

EDITORIAL: Preoxygenation 241
M. I Gold

ORIGINAL ARTICLES

Air embolism during total hip replacement: comparison of two surgical techniques 243
R. D. Evans, M. G. A. Palazzo and J. W. L. Ackers

Low-dose intrathecal diamorphine analgesia following major orthopaedic surgery 248
B. A. Reay, A. J. Semple, W. A. Macrae, N MacKenzie and I. S. Grant

Continuous thoracic extradural 0.5% bupivacaine with or without morphine: effect on quality of blockade, lung function and the surgical stress response 253
N. B. Scott, T. Mogensen, D. Bigler, C Lund and H. Kehlet

Electroacupuncture and postoperative pain 258
P. A. Christensen, M. Noreng, P. E. Andersen and J. W. Nielsen

Neuromuscular and cardiovascular effects of doxacurium in children anaesthetized with halothane 263
N. G. Goudsouzian, J. K. Alifimoff, L. M. P. Liu, V. Foster, B. McNulty and J. J. Savarese

Recovery of neuromuscular function after infusion or intermittent bolus doses of atracurium or vecuronium 269
K. L. Gordon and C. S. Reilly

Double burst stimulation (DBS): a new pattern of nerve stimulation to identify residual neuromuscular block 274
J. Engbæk, D. Østergaard and J. Viby-Mogensen

Train-of-four fade during onset and recovery of neuromuscular block: a study in non-anaesthetized subjects 279
G. A. Turner, J. D. Williams and D. J Baker

Effects of pipecuronium and pancuronium on the isolated rabbit heart 287
R. K. Deam and N Soni

Closed-loop feedback control of propofol anaesthesia by quantitative EEG analysis in humans 290
H. Schwilden, H. Stoeckel and J. Schuttler

Effects of halothane on somatosensory evoked potentials recorded in the extradural space 297
B A. Loughnan, M. J. King, E. M. Grundy, D. L. Young and G. M. Hall

General anaesthetic modification of synaptic facilitation and long-term potentiation in hippocampus 301
M B. MacIver, D. L Tauck and J. J Kendig

Effect of anaesthetic agents on bile flow and biliary excretion of ^{131}I-cholylglycyltyrosine in the rat 311
C. O. Mills, J F. Freeman, P J. Salt and E. Elias

RAPID COMMUNICATIONS

Maternal oxygenation during normal labour 316
P. N. Reed, A. D. Colquhoun and C. D. Hanning

Interaction of ketamine with atracurium 319
P. Toft and S. Helbo-Hansen

Cerebral blood flow during anaesthesia: influence of pretreatment with metoprolol or captopril 321
K. Jensen, L. Bunemann, S Risager and L. J Thomsen

Influence of suxamethonium on the action of subsequently administered vecuronium or pancuronium 324
K. Ono, N. Manabe, Y. Ohta, K Morita and F. Kosaka

CASE REPORTS

Natural killer cell activity in a patient undergoing resection of phaeochromocytoma 327
E. Tønnesen, F. Knudsen, H. K Nielsen and N J. Christensen

Anaesthetic management of a patient with Fascioscapulohumeral muscular dystrophy 331
D. L. Dresner and H. H. Ali

Complications of spinal anaesthesia following extradural block for Caesarean section 335
P. A. Stone, J. Thorburn and K. S. R Lamb

Bilateral pneumothorax following tracheal intubation 338
C. Biswas, N. Jana and S. Maitra

APPARATUS

Evaluation of the Ambu CPAP system 340
P. J. H. Venn

CORRESPONDENCE

The blood lancet in regional anaesthesia 348
Effect of suxamethonium given during recovery from atracurium 348

BOOK REVIEWS

Automation in Anesthesia—A Relief? 350
A Manual of Anaesthesia for Emergency Surgery 350
A Bibliography of References to Anaesthesia in the Australasian Medical Journals 1846–1952 350
Pulmonary Function Indices in Critical Care Patients 351

APRIL

EDITORIALS: I. Predicting the spread of spinal anaesthesia ... 353
J. A. W Wildsmith

II. Pulse oximeters. essential monitors with limitations ... 355
J. F Kidd and M. D. Vickers

ORIGINAL ARTICLES

Spread of spinal anaesthesia with plain 0.5% bupivacaine: influence of the vertebral interspace used for injection ... 358
M Tuominen, T. Tarvainen and P. H. Rosenberg

Effect of high thoracic extradural anaesthesia on ventilatory response to hypercapnia in normal volunteers ... 362
T Kochi, S. Sako, T. Nishino and T. Mizuguchi

Extradural pressure following the injection of two volumes of bupivacaine ... 368
D. L. Paul and J. A. W. Wildsmith

Doxacurium chloride: a preliminary clinical trial ... 373
R. P. F. Scott and J. Norman

Lung function in the supine and lateral decubitus positions in anaesthetized infants and children ... 378
A Larsson, C. Jonmarker, S. G E. Lindahl and O. Werner

Alfentanil obtunds the cardiovascular and sympatho-adrenal responses to suxamethonium-facilitated laryngoscopy and intubation ... 385
B. Scheinin, M. Scheinin, J. Vuorinen and L Lindgren

Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations ... 393
M Gottardis, K S. Khunl-Brady, W. Koller, G. Sigl and J. M. Hackl

Influence of preoperative gastric aspiration on the volume and pH of gastric contents in obstetric patients undergoing Caesarean section ... 397
J. G. Brock-Utne, C. Rout, J. Moodley and N. Mayat

Blood–brain barrier to pertechnetate following drug-induced hypotension ... 402
P. R Cook, D Myers, M Barker and J G. Jones

Effect of halothane, enflurane and isoflurane on body temperature during and after surgery ... 409
V. Ramachandra, C. Moore, N Kaur and F. Carli

Serial peak expiratory flow rates in mothers during Caesarean section under extradural anaesthesia ... 415
M. Gamil

Short term effect of nitrous oxide on methionine and S-adenosyl methionine concentrations ... 419
B D. Royston, T. Bottiglieri and J F. Nunn

Solubility of freon-22 in blood and lung tissue ... 425
P. J. Franks, R. H. Hooper and P R. M. Jones

Pretreatment with paracetamol inhibits metabolism of enflurane in rats ... 429
A. N. Hanna, J. S. McDonald, C. H. Miller jr and D. Couri

CASE REPORT

Anaesthetic management for Caesarean section in a patient with uncorrected truncus arteriosus ... 434
N. C. T Wilton, K B. Traber and L. S. Deschner

APPARATUS

Comparison of pulse oximeters: effects of vasoconstriction and venous engorgement ... 439
C. J. Wilkins, M. Moores and C. D Hanning

A new microprocessor-controlled anaesthetic machine ... 445
M. K. Sykes, B. R. Sugg, C. E. W Hahn, R K. Jackson and E. Palayiwa

Resistance to airflow in anaesthetic breathing systems 456
D. G. Martin, K. L. Kong and G. T. R. Lewis

Controlled ventilation with a Mapleson A (Magill) breathing system: reassessment using a lung model 462
C. K. G. Tyler, P. K. Barnes and M P. Rafferty

CORRESPONDENCE

Adverse reactions to atracurium ... 467
Suxamethonium and malignant hyperthermia ... 468
Predicting difficult intubation ... 469
Aid to intubation ... 469
The Recovery Interest Group ... 470

BOOK REVIEWS

An Introduction to Anaesthesiology ... 471
Surgery for Anaesthetists ... 471
Anaesthesia and Co-Existing Disease ... 471
Understanding Anaesthesia ... 472
Neonatal Anaesthesia ... 472
Anaesthesia for Thoracic Procedures ... 472
Anatomy for Anaesthetists ... 473

MAY

EDITORIAL: High frequency ventilation ... 475
M. K. Sykes

ORIGINAL ARTICLES

In vitro investigation of the priming principle for rapid neuromuscular block ... 478
R J. Storella, J. Jaffe, E. Mehr and H. Rosenberg

Antagonism of moderate degrees of vecuronium-induced neuromuscular block by small doses of neostigmine ... 483
R. A. Johnson and N. J. N. Harper

Comparison of mivacurium and suxamethonium administered by bolus and infusion 488
B. W. Brandom, S. K. Woelfel, D. Ryan Cook, S. Weber, D. M. Powers and J. N. Weakly

Transilluminated tracheal intubation 494
Q. P. Ainsworth and T. H. Howells

Pharmacokinetics of morphine following administration by the buccal route 498
A. R. Manara, M. P. Shelly, K. C. Quinn and G. R. Park

Safety and efficacy of a low volume extradural test dose of bupivacaine in labour 503
G. D. Prince, G. R. Shetty and M. Miles

Effect of time and adrenaline on the feto-maternal distribution of bupivacaine 509
F. Reynolds, R. Laishley, B. Morgan and A. Lee

Evaluation of "3 in 1" lumbar plexus block in patients having muscle biopsy 515
T. H. Madej, F. R. Ellis and P. J. Halsall

Incidence of arrhythmias in dental anaesthesia: a cross-over comparison of halothane and isoflurane 518
G. L. Hutchison, C. A. Davies, G. Main and I. G. Gray

Auditory evoked potentials during propofol anaesthesia in man 522
D. Chassard, A. Joubaud, A. Colson, M. Guiraud, C. Dubreuil and V. Bansillon

Effect of ketanserin on sodium nitroprusside requirements, arterial pressure control and heart rate following coronary artery bypass surgery 527
N. B. A. Hodsman, J. R. Colvin and G. N. C. Kenny

Effects of propofol on pulmonary and systemic arterial pressure-flow relationships in hyperoxic and hypoxic drugs...... 532
R. Naeije, P. Lejeune, M. Leeman, C. Melot and T. Deloof

Is there a relationship between masseteric muscle spasm and malignant hyperpyrexia? 540
A. S. Christian, F. R. Ellis and P. J. Halsall

Venous sequelae following i.v administration of diclofenac................................ ... 545
W. I. Campbell and C. H. Watters

Electroencephalographic effects of laudanosine in an animal model of epilepsy 548
A. Tateishi, M. H. Zornow, M. S. Scheller, P. C. Canfell

Effect of nicardipine infusion on the release of glutathione S-transferase following halothane anaesthesia 553
D. C. Ray, G. J. Beckett, J. D. Hayes and G. B. Drummond

Effect of diltiazem on porcine malignant hyperpyrexia induced by suxamethonium and halothane 560
P. S. Foster, K. C. Hopkinson and M. A. Denborough

Effect of diltiazem and dantrolene on the contractility of isolated malignant hyperpyrexia-susceptible porcine skeletal muscle 566
P. S. Foster and M. A. Denborough

RAPID COMMUNICATION

Plasma concentrations of catecholamines following intraocular irrigation with adrenaline 573
D. Fell, A. P. Watson and N. Hindocha

CASE REPORT

Perioperative complications following the use of vancomycin in children: a report of two cases. . 576
C. J. Best, M. Ewart and E. Sumner

CORRESPONDENCE

Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia 578
Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy.......... 579
Parkinsonism and the anaesthetist. 580
Prostaglandins and the lower oesophageal sphincter 581

BOOK REVIEWS

Obstetric Anesthesia: The Complicated Patient 582
Yearbook of Critical Care Medicine, 1988.. 582
A History of Longworth Scientific Instrument Co. Ltd 583
Anyone Can Intubate 583
Perspectives in Critical Care Medicine 583
Current Practice in Anesthesiology 584

JUNE

EDITORIAL: The safety of new drugs 587
C. J. Hull

ORIGINAL ARTICLES

Atracurium—a post-marketing surveillance study: Methods and U.S. experience 590
H. Jick, E. B. Andrews, H. H. Tilson, M. Pfanschmidt, C. Branche, A. M. Walker and D. H. Lawson

Atracurium—a post-marketing surveillance study: U.K. study and discussion 596
D. H. Lawson, G. M. Pace, R. J. Glavin, E. B. Andrews, C. Branche, H. Tilson and H. Jick

Effect of nalbuphine hydrochloride on the ventilatory and occlusion pressure responses to carbon dioxide in volunteers 601
G. C. Pugh, D. T. Brown and G. B. Drummond

Pharmacokinetics of alfentanil during and after a fixed rate infusion 610
H. van Beem, A. Van Peer, R. Gasparini, R. Woestenborghs, J. Heykants, H. Noorduin, J. van Egmond and J. Crul

Use of magnesium sulphate in the anaesthetic

management of phaeochromocytoma: a review of 17 anaesthetics 616
M. F. M. James

Retrospective study of early postoperative convulsions after intracranial surgery with isoflurane or enflurane anaesthesia 624
A. R. Christys, E. Moss and D. Powell

Comparison of the effects of high frequency oscillation and controlled mechanical ventilation on hyaline membrane formation in a rabbit model of the neonatal respiratory distress syndrome 628
D J. Niblett, B. K. Sandhar, M. S Dunnill and M. K. Sykes

Percutaneous anterior approach to the coeliac plexus using ultrasound 637
A. Montero Matamala, F. Vidal Lopez, J. L. Aguilar Sanchez and L. Donoso Bach

Controlled trial of extradural bupivacaine with fentanyl, morphine or placebo for pain relief in labour 641
J. D. Lirzin, P. Jacquinot, P. Dailland, J. C. Jorrot, J. Jasson, M. L. Talafre and C. Conseiller

Awareness following different techniques of general anaesthesia for Caesarean section 645
A. Baraka, F. Louis, R. Noueihid, M. Diab, A. Dabbous and A. Sibai

Neurobehavioural effects of propofol on the neonate following elective Caesarean section....... 649
D. Celleno, G. Capogna, M. Tomassetti, P. Costantino, G. Di Feo and R. Nisini

Dose–response curves for suxamethonium in neonates, infants and children...... 655
G. Meakin, E. P. McKiernan, P. Morris and R. D. Baker

Use of atracurium or vecuronium to prolong the action of tubocurarine 659
C. M. Middleton, B J. Pollard, T. E. J. Healy and B. Kay

Doxapram and the neuromuscular junction 664
B. J. Pollard, N. P. C. Randall and B J. Pleuvry

Inhalation anaesthetics decrease calcium content of cardiac sarcoplasmic reticulum.. 669
M. Katsuoka and S. T. Ohnishi

Antroduodenal mobility, pH and gastric emptying during balanced anaesthesia: comparison of pethidine and fentanyl 674
B. A. Schurizek, L. H. O. Willacy, K. Kraglund, F. Andreasen and B. Juhl

Effect of atracurium and laudanosine on the release of ^{3}H-noradrenaline 683
M. Kinjo, H. Nagashima and E. S Vizi

Effect of propofol on the malignant hyperthermia susceptible pig model 691
R. Krivosic-Horber, H. Reyfort, M. C. Becq and P Adnet

RAPID COMMUNICATIONS

Effect of general anaesthesia on the magnetic resonance imaging signal from the brain 694
A. Whitfield and R. H. B. Douglas

Accelerated recovery from combined atracurium–vecuronium neuromuscular block.............. 697
J. A. Stirt

CORRESPONDENCE

The anaesthetist's activities in the operating theatre 700

BOOK REVIEWS

Imaging and Labelling Techniques in the Critically Ill 701
Pocket Manual of Anesthesia 701
Acupuncture Treatment and Anaesthesia 702
Clinical Anatomy for Anesthesiologists 702
Index to Volume 62.......... 703

"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL I

AIRWAYS REVISITED

The recognition and management of the difficult airway has been a source of great discussion in the anaesthetic literature. If all difficult airways could be predicted confidently in the preoperative period, anaesthetists could plan the safest and most effective way of managing tracheal intubation. This would identify a patient whose trachea could not be intubated and perhaps obviate the possible disastrous consequences of failure to intubate, particularly in a patient presenting for emergency surgery.

Currently, in the majority of cases, a clinical history and examination of the patient remain the major method of alerting the anaesthetist to possible difficulty in performing tracheal intubation. However, in the past decade considerable strides have been made in predicting difficult intubation.

Mallampati and his associates [1] have developed a useful clinical test. The patient was seated at 90° to the horizontal, facing the anaesthetist, and invited to extrude the tongue as far as possible, permitting allocation of the patient to one of three classes. In class one, the faucial pillars, soft palate and uvula were seen. In class two the pillars of the fauces and soft palate were seen, but the uvula was masked by the base of the tongue. In class three, only the soft palate was seen. At subsequent tracheal intubation, the amount of glottis visible was graded according to the classification of Cormack and Lehane [2]. In essence, Mallampati found that the less that was visible at the back of the mouth, the more difficult was the subsequent tracheal intubation. Samsoon and Young [3] developed this theme further and introduced a class four in which the soft palate was not visible. In their retrospective study they found a positive correlation between abnormal anatomy of the oro–pharynx and the degree of difficulty at subsequent intubation.

In these two studies, it was suggested that either the tongue was enlarged considerably or the surrounding structures were unusually small. Whichever is correct is irrelevant, because in both cases the tongue overhangs the entrance to the glottis, thereby making it more difficult to accomplish easy intubation.

Wilson and his colleagues [4] measured 14 variables in the head and neck. After application of discriminant analysis to the accumulated data, five risk factors were identified. These included body weight, extent of head, neck and jaw movement, and presence of a receding mandible and buck teeth. These risk factors were accorded scores of between 0 and 2 and the net sum, termed the risk score, varied between 0 and 10. The greater the risk score, the greater is the potential for difficulty in intubation. Most anaesthetists would certainly recognize these factors as causes of potential difficulties, and it is pleasing to note that what has been taught in clinical practice bears a strong relationship to scientific studies in this field.

In this issue of the Journal, Horton, Fahy and Charters [5] have defined the angles of the head and neck for optimum positioning to perform tracheal intubation. These particular values may ultimately become the standard measurements for future research in this field.

Although these observations and measurements do not always predict difficult intubation, they are useful in approximately 80% of patients. What is more crucial is that these data may be obtained at the bed side and augment the history and clinical examination. It is clear, therefore, that the best prediction of difficult intubation is achieved when the anaesthetist visits the patient before operation. It would also seem prudent that the anaesthetist who is directly responsible for anaesthesia should personally visit the patient. In addition, training young anaesthetists to make these observations and measurements at their preoperative visits would be important, as they could request the help of a senior colleague before and not after attempting to perform tracheal intubation.

How should we manage a difficult intubation?

In general, if a difficult intubation is predicted, most anaesthetists would prefer to intubate the trachea using local anaesthetic techniques. The advent of the fibreoptic bronchoscope has made access relatively easy through either the nose or mouth into the larynx. Various aids to assist this process are also available commercially. Retrograde intubation, based on the original technique of Waters [6], from below the larynx has been well documented, while transtracheal ventilation follows the technique developed by Leyman [7]. However, these latter two techniques are not taught widely in the United Kingdom, possibly because it is considered unethical to perform retrograde intubation or establish transtracheal ventilation in a normal patient. The lack of teaching of fibreoptic techniques is almost certainly the result of the high costs involved in purchasing these bronchoscopes and the paucity of anaesthetists who have obtained training in their use.

Despite correct preoperative assessment, there still remains a number of patients whose trachea cannot be intubated following induction of anaesthesia and the administration of neuromuscular blocking drugs. If the airway is not managed correctly under these circumstances, the results may be disastrous. Many failed intubation regimens have been proposed, for example those of Tunstall [8] and Rosen [9]. Although these recommendations are designed primarily for obstetric patients, they are applicable equally to other types of patients undergoing emergency procedures.

These circumstances occur only rarely, which carries disadvantages in terms of training and experience. Traditionally, the anaesthetist is trained to intubate the trachea during his early career on elective theatre lists and only very rarely does s/he encounter a very difficult intubation (between 1 and 3% of all patients). It is important, therefore, that the trainee should be instructed to cope with a difficult airway as part of routine early training.

How can such a programme be achieved? Certainly, to wait for difficult intubations to present themselves on elective lists would be unproductive. The solution may be to use models which can simulate such circumstances [10], traditional teaching methods, simulated difficult intubation in normal patients [11] and the preparation of suitable video programmes. Each training department should possess such aids so that young anaesthetists and, indeed, experienced anaesthetists would be able to develop, practise and refresh their skills. In addition, algorithms have been produced to indicate what alternative courses of action are available [12] in an emergency situation.

Another approach is that suggested by Ovassapian and colleagues in this issue [13]. They have proposed a rather revolutionary way of dealing with patients considered to be at high risk of aspiration while removing the possibility of being unable to accomplish intubation. They intubated the trachea of 121 awake ptients under direct vision using either oral or nasal fibreoptic techniques. These patients received local anaesthesia to the larynx and upper trachea either by direct spraying or by cricothyroid puncture. The aim was to produce analgesia in the upper respiratory tract, leaving the rest of the tract largely unaffected. Should such a patient subsequently inhale, the lower respiratory tract reflexes should induce coughing, thereby protecting the lower airway and lungs. It is interesting to note that, despite the one occasion when a patient vomited a large quantity of fresh and clotted blood, there was no evidence of pulmonary aspiration.

It seems that this method has potential. However, as only 121 patients were included in the study and the accepted incidence of difficult intubation varies between 1 and 3%, it may be premature to adopt this technique until its proponents have had experience of many thousands of cases. Their call for a controlled clinical trial comparing the three possible methods for achieving intubation in emergency cases is also premature, as anaesthetists must be able to use a fibreoptic bronchoscope as expertly as they use a laryngoscope. It is likely that this will take some time to achieve. However, chest physicians have quickly become very adept at fibreoptic bronchoscopy. There is no reason why anaesthetists should not achieve the same degree of skill very rapidly. Having gained much experience, a controlled clinical trial of intubation in the emergency patient might then be considered.

Irrespective of research potential, it is of paramount importance that anaesthetists learn to use a fibreoptic bronchoscope competently. To achieve this goal requires a great deal of investment in both training and equipment. The practice of anaesthesia has relied increasingly over the past decade on research and the application of modern technology. The fibreoptic bronchoscope represents one of the latest developments and the advantages that can be gained from its correct use should be pursued vigorously.

Confirmation of successful intubation has also been examined closely in the past few years. The sight of the tracheal tube passing between the cords, checking with a stethoscope that there is air entry into both lungs and the absence of cyanosis have been the traditional criteria for successful intubation in the majority of patients. However, even experienced anaesthetists have occasionally found these criteria to be misleading. Other methods of confirmation, such as the tactile method recommended by Charters and Wilkinson [14] and the aspiration method of Wee [15] have been advocated recently, but increasing concern regarding infection may render these methods less acceptable. However, if a capnograph attached to a tracheal tube shows repeated movements between zero and 4–6% carbon dioxide with ventilation, the tracheal tube is in the correct location. The fibreoptic bronchoscope is also of great assistance with confirmation. If a fibreoptic bronchoscope is passed through the tracheal tube, visualization of the carina confirms that tube is in the trachea.

An editorial on the recognition and management of a difficult intubation would not be complete without repetition of the old adage that *a patient does not die from failure of tracheal intubation but from failure of oxygenation.* If the anaesthetist is in any doubt that the tube is not in the trachea, s/he should remove it and ventilate the patient's lungs with oxygen by whatever means are available. Rapid and effective action to achieve this aim will be pursued by the trainee anaesthetist under conditions of potential stress and panic only if s/he has received sound and continuous training in the management of tracheal intubation.

R. S. Vaughan

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EDITORIAL II

ANAESTHESIA OF THE SKIN

Anaesthetists are particularly aware of the pain produced by an i.v. injection, especially when dealing with children. Many older text books of paediatric anaesthesia recommended the use of a small 26- or 27-gauge needle in order to minimize pain, but in order to give large volumes of fluid rapidly in an emergency it is preferable to insert a larger sized cannula which is retained *in situ* throughout the period of anaesthesia. This requirement for safety has to be balanced against ensuring that a child's stay in hospital is as atraumatic as possible. Thus the recent introduction of a preparation, EMLA (Astra Pharmaceuticals), to provide topical anaesthesia of the skin before venepuncture has been beneficial, particularly in paediatric practice.

EMLA is a Eutectic Mixture of Local Anaesthetics, incorporating lignocaine and prilocaine to provide approximately 80% active local anaesthetic in each droplet, compared with only 20% if lignocaine alone is emulsified. It is applied as a layer on the proposed site(s) of injection and an occlusive dressing placed over it. The dressing retains the cream *in situ*; both are removed before venepuncture. It has been available for several years and was marketed in the U.K. in 1986. The use of EMLA cream is increasing, both in paediatric practice for routine taking of blood samples and in anaesthetic practice as part of premedication before i.v. induction of anaesthesia. Older children now appear to be requesting such pretreatment, having seen it used on their peers; it may be only a short time before some adult patients make similar requests.

The use of topical anaesthesia for the skin has been investigated for more than 30 years. To be effective, a local anaesthetic preparation should contain sufficient concentration of the active agent in the emulsion applied to the skin; it should penetrate intact skin adequately, and it should exhibit a rapid onset of action with prolonged analgesic effect. However, these properties would lead to systemic absorption and therefore the agent should possess low toxicity.

The rate of onset of analgesia varies following dermal application of local anaesthesia. In 1974, Lubens and colleagues [1] described their experience of more than 11 years use of a patch consisting of 30% lignocaine cream. It was necessary for this to remain in place for 2 h to guarantee analgesia lasting longer than 30 min. Only one study has assessed the minimal necessary time of application of EMLA cream before venepuncture and found it to be approximately 60 min [2]. Other studies, mostly with children aged 4–17 yr have used this timing and obtained favourable results. One group recently reported the use of EMLA cream in younger children, aged 1–5 yr [3], and found no advantage in leaving the cream *in situ* for longer than 30 min. Therefore, age and skin type or thickness may be important in the speed of onset of analgesia.

The plasma concentrations of lignocaine [4] and both lignocaine and prilocaine [5] have been measured following application of EMLA cream and it seems that toxic concentrations of the agents are not normally reached. Enberg and colleagues [5] examined children aged 3–12 months and found both local anaesthetics were detectable in blood (drawn from a distant site) for up to 8 h and there were no signs of toxicity. The current data sheet does not recommend the use of EMLA in infants (i.e. younger than 12 months of age).

Recent work *in vitro* [6] has suggested that amethocaine is superior to several other local anaesthetic agents, including lignocaine, for dermal anaesthesia. The same workers have pursued this further by comparing EMLA with the amethocaine preparation, and the results are published in the present issue of the Journal [7]. This study confirmed that the amethocaine provided significant topical anaesthesia, and did so more quickly than EMLA (35 min compared with 67 min), and that the analgesia lasted longer (more than 4 h compared with 1 h). This amethocaine preparation is obviously promising, but it requires further assessment, in children in addition to adults, both to confirm its efficacy and to determine optimum dosage and time of application. Amethocaine is a potent local anaesthetic and has been noted in the past for its toxicity.

Therefore, careful assessment of possible side effects should be made, including measurement of plasma concentrations of amethocaine.

Topical anaesthetics have been used for minor surgery for many years, particularly in plastic surgery. It would be illogical in anaesthetic practice to limit their use to venepuncture. Application before extradural/spinal anaesthesia or any type of regional block may be useful, as it is the infiltration of the skin with local anaesthetic which is often the most painful part of the procedure. Thus there is scope for widespread use of dermal anaesthetic preparations.

There are presently very few reported side effects from EMLA cream. The most common problems reported include transient local skin blanching or erythema; more may become apparent with increased and enthusiastic use. Dermal anaesthetic preparations should be prescribed with the care applied to administration of all medication. Although EMLA is, apparently, safe enough to allow much leeway with dosage, there has already been one report of methaemoglobinaemia in a small child, when 5 g of the cream was applied and left in place for 5 h [8].

At this relatively early stage in their clinical life, there is still the need, therefore, for further assessment of these preparations. Firm recommendations should be made, based on sound scientific evidence, for what may otherwise become a "little dab of cream", analogous to the infamous "quick whiff of gas".

S. Coley

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DEFINING A STANDARD INTUBATING POSITION USING "ANGLE FINDER"

W. A. HORTON, L. FAHY AND P. CHARTERS

SUMMARY

Study of patients who exhibit only limited morphological abnormality yet present difficulty with direct laryngoscopy is facilitated by a standard intubating position. The "Angle Finder" instrument allows implementation of a simple reproducible geometric standard which is applied easily in formal research work and in clinical practice and teaching. The proposed standard relates to the curved (Macintosh) laryngoscope blade and a supine patient. The lower neck flexion is 35° and extension of the plane of the face 15°, each angle measured relative to horizontal. Initially, the standard was derived from a review of the literature, then validated in a study of the intubating practices of 10 senior anaesthetists. A more detailed study of 10 normal volunteers confirmed reproducibility and, for nine patients with a history of difficult direct laryngoscopy, the standard was shown to be appropriate.

It has been estimated that the incidence of difficult laryngoscopy is approximately 1 in 2000 [1]. Because it is uncommon, studies of relevant factors have involved only small numbers of patients [2–4]. Comparison between such studies is limited by the absence of an agreed standard intubating position. It would be unexpected for any one position to be appropriate for the variety of conditions that may be encountered. In practice, however, attention is directed normally to patients in whom there is either limited deformity or no abnormality at routine preoperative assessment.

The aim of this study was to determine a research standard suitable for such circumstances. The proposed standard evolved from the traditional notion of flexion of the neck and extension of the head and from relatively recent work by Alexopoulos and colleagues [5]. Their study suggested that the lower neck (from the level of the cricoid plate to 40 mm below this) was relatively stable during flexion/extension movements of the head. It seemed possible, therefore, that a standardized position might require definition of just the angles of flexion of the lower neck and extension of the head. The "Angle Finder" instrument facilitates easy alignment by this means.

PATIENTS AND METHODS

Angle Finder instrument

This simple general purpose instrument is shown in figure 1. It consists of an "L-square" section which moves along a metallic ruler. Housed in the body of the L-square is a circular dial around which an eccentrically weighted pointer rotates freely. The pointer responds to gravity, while the dial is fixed and rotates with the ruler. When the ruler is horizontal the pointer reads zero degrees. To ensure free movement of the pointer, the instrument should be kept in a vertical plane.

Proposed standard intubating position

For a curved (Macintosh) laryngoscope blade with the patient supine, the lower neck is flexed 35° relative to horizontal and the plane of the face extended 15° similarly (fig. 2).

Neck flexion is related to the anterior surface of the trachea, from the level of the cricoid cartilage down to the sternal notch. In thin individuals in

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This article is accompanied by Editorial I.

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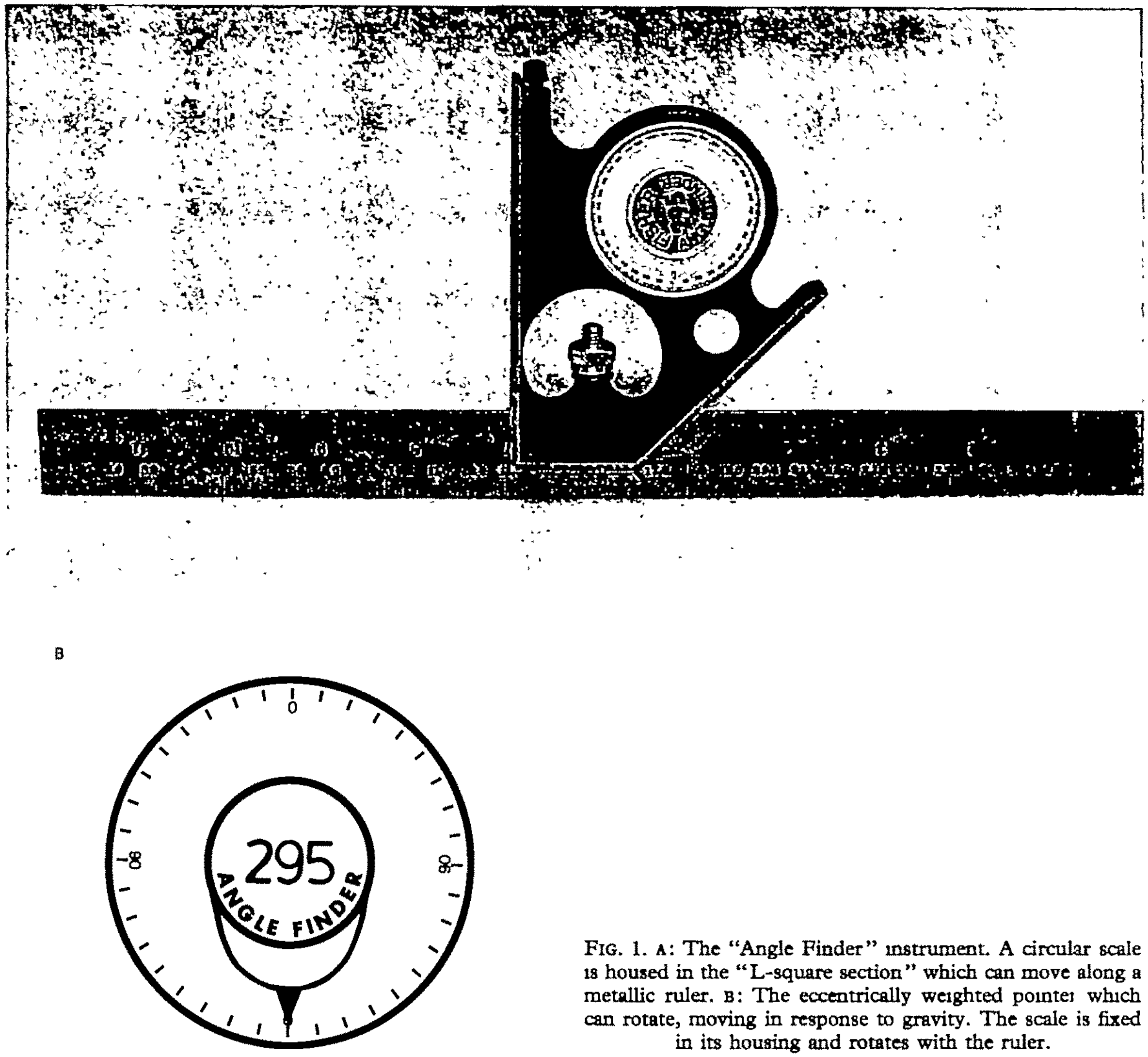

FIG. 1. A: The "Angle Finder" instrument. A circular scale is housed in the "L-square section" which can move along a metallic ruler. B: The eccentrically weighted pointer which can rotate, moving in response to gravity. The scale is fixed in its housing and rotates with the ruler.

whom the trachea is obviously superficial, aligning the Angle Finder with it is easy. When the sternomastoids are prominent or neck swellings, obesity or short neck make this alignment difficult, the instrument is lined up with the cricoid cartilage above and the depth of the sternal notch below.

Head extension is defined relative to the plane in which the supraorbital, infraorbital and mental foramina lie. Normally, these foramina are aligned in both frontal and lateral aspects [6]. In certain conditions where difficult intubation occurs (e.g. receding mandible), alignment fails. Appropriate allowances (which were not required in any subjects in the present study) are facilitated by drawing the landmarks. When the mouth is opened the mental foramen loses alignment, so it is ignored when measuring extension at laryngoscopy (fig. 3).

Observed intubation study

Ten senior anaesthetists (two senior registrars and eight consultants) were observed during 10 laryngoscopies in the course of their normal clinical practice. In all but one, competitive neuromuscular blocking drugs were used. After induction and before intubation the initial neck flexion and face-plane extension were measured as

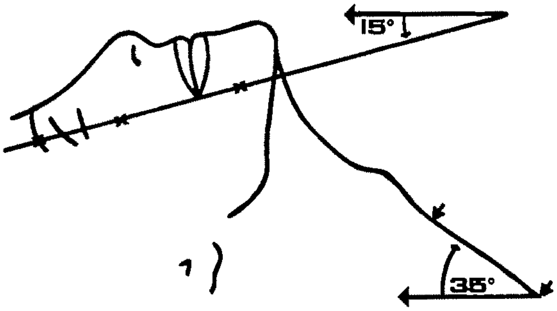

FIG. 2. The standard intubating position (SIP). The supra-orbital, infraorbital and mental foramina are labelled x and shown to be in line at an angle of 15° of declination. The line of neck flexion is defined by two points: the upper is the cricoid and the lower is level with the lowermost depth palpable in the sternal notch.

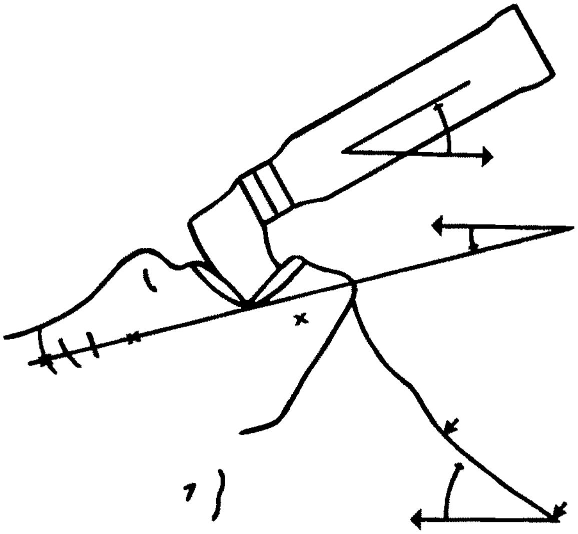

FIG. 3. Angles measured at intubation. The neck flexion is equivalent to the SIP situation. The line of the face-plane is similar, but note that because the mouth is open the mental foramen is now irrelevant. The angle of the laryngoscope handle is the elevation from horizontal.

for the standard position (fig. 2). When laryngoscopy was effected and the tracheal tube about to be passed, the anaesthetist paused momentarily to allow the initial measurements to be repeated and the angle of the laryngoscope handle was noted also (fig. 3).

Reproducibility and relevance to difficult intubation

Because the disposition of the upper neck is not defined by the proposed standard, 10 young adults (five male; mean age 32 (SD 6) yr) acted as controls to determine reproducibility. In each subject direct laryngoscopy was known not to be difficult. The test used was simply to alter the height of a rigid base on which the head rested and make repeated observations to determine the range of base height over which the standard position could be achieved.

Relevance to subjects difficult to intubate was assessed by examining nine patients (six male; mean age 53 (18) yr) in whom difficulty with intubation had been documented during anaesthesia in the preceding 12-month period. None of these anaesthetics was associated with pregnancy. In addition to determining whether or not the standard position could be achieved, overall head and neck flexion/extension movements as used in routine preoperative assessment [7] were measured using the Angle Finder.

RESULTS

In the observed intubations, study angles were measured to the nearest 5° increment (0, 5, 10 *etc.*), relative to 0° horizontal. Angles of face-plane extension were denoted negative when the face sloped upwards rostrally. The overall measurements before and at intubation for neck flexion are shown in figure 4 and those for face-plane extension in figure 5. In each subject the peak value increased at intubation and the distribution became more Normal. Differences between the two sets of values were attributable to the initial laryngoscope blade placement rather than any subsequent manipulations to improve on the view obtained. At intubation the overall mode value for flexion was 35° (in 42/100) and for face-plane extension 20° (in 28/100). The 35° neck flexion was also the individual mode for 7/10 anaesthetists.

All but three measurements of laryngoscope handle angle were in the range 20–50°, the mode value was 30° and the mean 35.5 (9.2)°. The neck and face-plane angles at intubation and handle angles were subjected to correlation coefficient analysis. No correlation was shown for neck flexion and the angle of the handle ($P > 0.1$). A significant relationship was found for neck flexion and face-plane extension ($P < 0.01$) and a highly significant relationship occurred between the angle of the handle and face-plane extension ($P < 0.001$). The linear equation derived for this latter relationship was:

$$(\text{angle of face extension})^\circ = 0.30 \times (\text{angle of handle})^\circ + 9.7.$$

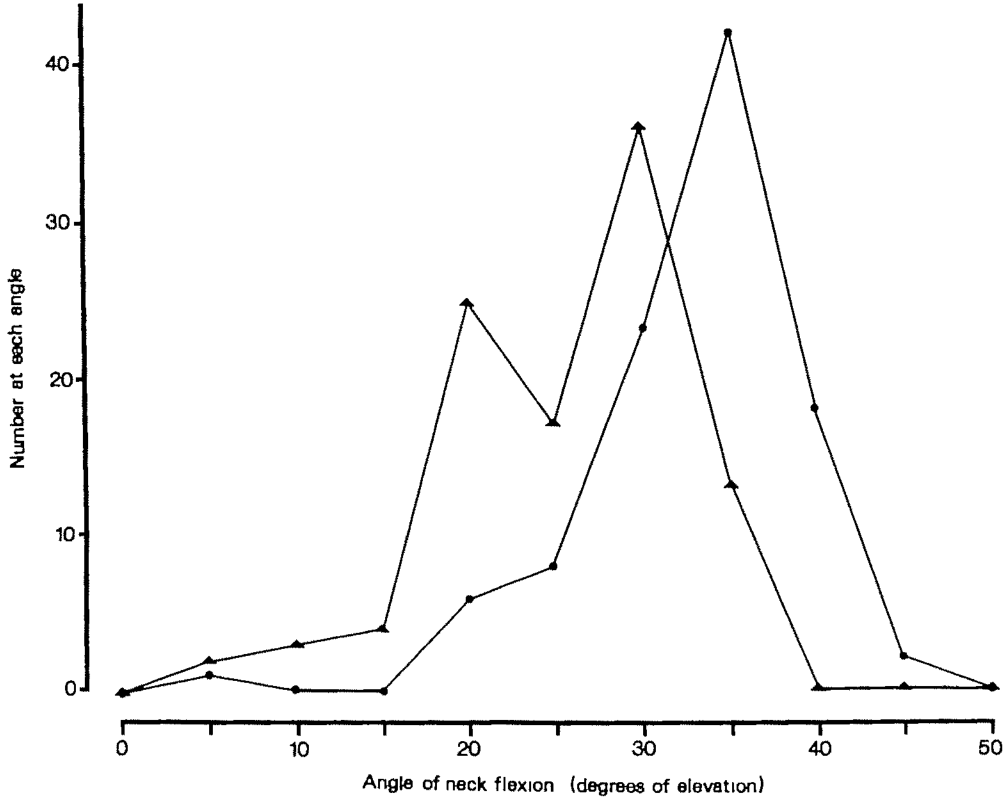

FIG. 4. The frequency of each angle of neck flexion (degrees of elevation from zero horizontal) before laryngoscopy (▲) and at the moment of full glottic exposure (●).

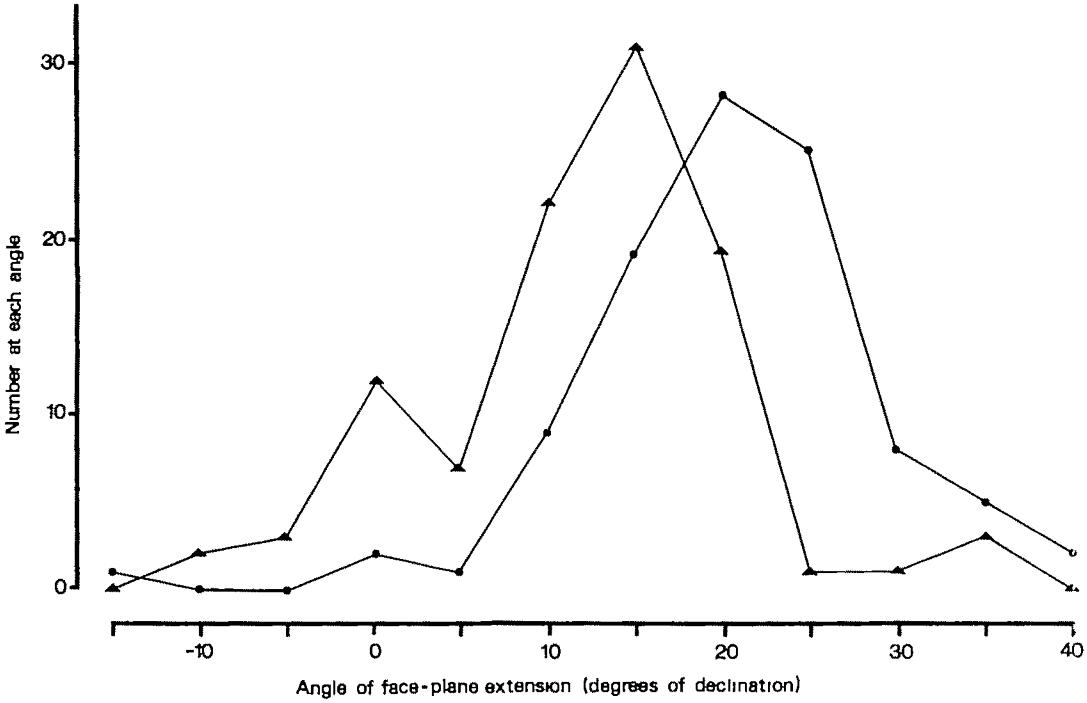

FIG. 5. The frequency of each angle of face-plane extension (degrees of declination from zero horizontal) before laryngoscopy (▲) and at the moment of full glottic exposure (●).

TABLE I. *Reproducibility of standard intubating position (SIP) in control subjects*

Subject No.	Overall head and neck movements (°)			Difficulty positioning in SIP	Height range of head base for SIP (mm)		
	Flexion	Extension	Range		Min.	Max	Range
1	60	70	130	No	53	58	5
2	70	70	140	No	44	50	6
3	70	85	155	No	31	37	6
4	55	75	130	No	56	60	4
5	65	100	165	No	64	67	3
6	60	70	130	No	64	71	7
7	65	65	130	Yes	—	—	—
8	65	85	150	Yes	—	—	—
9	55	85	140	No	46	51	5
10	60	90	150	No	62	67	5
Mean	62.5	79.5	142	—	52.5	57.6	5.1
n	10	10	10	—	8	8	8

TABLE II. *Standard intubating position (SIP) and neck movements—difficult intubation patients.* ***$P < 0.001$ *compared with control subjects*

Patient No.	Overall neck movements (°)			Difficulty positioning in SIP
	Flexion	Extension	Range	
1	50	60	110	Yes
2	55	30	85	Yes
3	45	50	95	Yes
4	45	45	90	No
5	40	65	105	No
6	45	65	110	No
7	50	60	110	No
8	50	50	100	Yes
9	45	50	95	No
Mean	47.2***	52.8***	100***	—

Provided that face-plane extension was taken as 15° to the nearest 5°, all controls (table I) and patients (table II) could be placed in the standard position. At 35° of neck flexion, certain individuals in both groups could not manage the full 15° extension, but in each subject the extension achieved was nearer 15° than 10°. This limitation was evident in 4/9 of the subjects in whom laryngoscopy was difficult and in 2/10 controls.

In the eight control subjects in whom the full position was achieved, the inclusive range of base height under the head for which the position was possible is shown in table I. The inclusive range of base height was never greater than 8 mm (measurements were to the nearest 1 mm). The overall range for base height was 31–71 mm and the mean mid-range value was 55 mm. Overall neck flexion/extension measurements are also recorded in tables I and II. With one exception, all were within the range usually quoted: 90–165° [8].

DISCUSSION

The case for a standard intubating position in the investigation of patients presenting difficult direct laryngoscopy with no gross morphological abnormality should be considered self evident. While many studies [2, 3, 9] have promoted indices of abnormality derived from radiographs, certain of these measurements, such as "atlanto-occipital gap", vary with posture [10].

The present investigation began with a detailed analysis of the relevant literature to derive angles for neck flexion and face-plane extension (table III). Surprisingly few reference works had illustrations of actual laryngoscopy and diagrams or photographs of suggested postures were common. As the present study shows, laryngoscopy itself alters positioning, even when considered placement has preceded it. Early references often had gross anatomical inaccuracies and so were excluded as, in general, were citations of previous work. The literature review suggested 35° for neck flexion, but the angle of face-plane extension was less obvious—15° was a compromise. While it was felt that a modest extension was common practice, it was also considered important not to define a standard that excluded too many of the relevant cases.

In the observed intubation study, the anaesthetists were not aware of the details of the proposed standard. The prevalence (42/100) of

TABLE III. *Analysis of relevant literature*

Source	Year	Material	Posture only or actual laryngoscopy	Blade type	Angles Neck/Face (°)	Original author comment
Jackson [11]	1913	Photograph	Laryngoscopy	Laryngeal speculum	20/55	Patient intolerant of bad positioning (local anaesthesia).
Jackson, Jackson [12]	1934	Diagram	Posture	Laryngeal speculum	35/35	Neck not naturally horizontal when emerging from thorax.
Gillespie [13]	1941	Diagram	Posture	Straight	40/−5	Head raised > 10 cm above table.
Bannister, Macbeth [14]	1944	X-rays	Laryngoscopy	Straight	40/0	Two pillows for neck flexion.
Boulton, Cole [15]	1966	Diagram	Posture	Curved	35/25	Pillow should be removed.
Cullen, Larson [16]	1974	Diagram	Posture	Curved and straight	25/0	Too much head extension pushes larynx anteriorly.
Thornton [17]	1974	Photograph	Posture	Curved	35/25	Additional extension of neck when blade in mouth.
Applebaum [18]	1976	Photograph + xeroradiograph	Laryngoscopy	Curved	35/20	Extreme head flexion or extension does not help.
Murrin [19]	1985	Photograph	Posture	Curved	35/0	Pillow flexes lower cervical spine. Extension via finger on upper teeth.
Present study	1988	(Patients)	Laryngoscopy	Curved	35/15	Idealized posture and practice not necessarily the same.

the 35° neck flexion at laryngoscopy was a useful confirmation of the literature-derived value. Extension showed a wider "spread" and a peak at 20°. The more exaggerated extension manoeuvres which certain authors have advocated [17, 20, 21] were not evident.

The anticipated limitation of extension in the subjects of known difficult laryngoscopy was observed. In effect, four of these nine subjects came within the definition of the standard only by taking the extension angle to the nearest 5°. A similar limitation in two of 10 control subjects was unexpected. This difference was not significant. (Subsequent work has confirmed this limitation occurs in 21 % of normal individuals, so of itself it would not predict the difficult subject.)

It could be argued that an extension of 10° might have been a better choice. However, in only 13 of the 100 observed intubations was extension 10° or less and literature citations of such limited extension are not as frequent as table III might imply. Even the photograph referred to in Murrin's work has accompanying diagrams with 30–35° of extension. A recent radiological investigation [22] also confirmed the importance of extending the atlanto–occipital joint for adult intubation. The 15° extension is, therefore, suggested to be an optimal compromise.

Forty-five degrees has been suggested as an appropriate angle of elevation for the laryngoscope handle [18, 23]. In this study the commonest angles were 30° (27/100) and 35° (24/100). Our linear regression equation shows that, as the angle of elevation of the handle decreases (towards 14°), so the face-plane becomes more nearly parallel to it. (The handle effectively draws the face-plane into line behind it.) Leverage forces on the upper incisors would be expected to be less the more nearly parallel these are, so an angle of 30° would be an advantage over the previous recommendation.

Reproducibility was evident clinically and in the study. The control subjects were chosen because they were relatively young and neck mobility would be expected to decrease with age. Certain of the controls had long thin necks and it was important to ensure the lower neck remained straight, to avoid an excessive range of possible positioning. When compared with neck length measurements, the range of head base height was equivalent to an accuracy of less than ± 1° in the neck flexion angles. Radiologically, cervical spine movements can have complex normal variations, particularly in younger patients [24, 25]. More exact reproducibility would seem unlikely, even if a larger number of parameters was used in an alternatively defined standard.

The overall flexion and extension angles shown in tables I and II are measured rapidly using the Angle Finder and it can be used for routine preoperative assessment. The mean values for flexion and extension were less in the patient group than in the control subjects ($P < 0.001$ in each case, by Student's t test), but the groups were not matched for age and this could explain the difference. Nevertheless, it is suggested that these results are of interest and warrant further investigation.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the willing help from senior colleagues who were involved in the observed intubations study, and junior colleagues who agreed to act as controls.

The authors have no financial interest in the Angle Finder instrument. It is made for general engineering use, but for widespread use in operating theatres the company has agreed that it can be made washable and have its sharp corners modified. The instrument reference number is 295 and the manufacturer's address is: Fisher Instruments, Pysons Industrial Estate, Broadstairs, Kent, England.

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AWAKE FIBREOPTIC INTUBATION IN THE PATIENT AT HIGH RISK OF ASPIRATION

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SUMMARY

This report describes our experiences with 129 awake oral and nasal fibreoptic intubations in 123 patients considered to be at high risk of aspiration of gastric contents. I.v. sedation was used on all but six occasions. Local anaesthesia was applied to the larynx and trachea through the working channel of the fibrescope on 85 occasions, and by transtracheal injection on 29. Rigid laryngoscopy was necessary after fibreoptic laryngoscopy failed in one patient (with a bleeding peptic ulcer) who vomited a large amount of fresh and clotted blood. No other patient regurgitated during the procedure, and no patient developed evidence of aspiration.

Aspiration of gastric contents remains an important cause of morbidity and mortality in patients requiring general anaesthesia for emergency surgery [1–3]. None of the anaesthetic techniques for preventing this complication is either completely successful or always applicable [2]. However, isolation of the trachea from the gastrointestinal tract with a cuffed tracheal tube is perhaps the best method for preventing aspiration. There are two techniques, each associated with its own hazards, used commonly for this purpose [2–4]. First, a rapid sequence induction and tracheal intubation following pre-oxygenation and cricoid pressure [4–6]; and second, intubation of the trachea in an awake patient using a rigid laryngoscope [7–9]. There do not appear to be any well controlled clinical trials comparing these two techniques.

Depending on the details of its performance, the hazards and difficulties of a rapid sequence induction and intubation include: incomplete relaxation; coughing during intubation; problems with cricoid pressure; regurgitation; cardiovascular changes; mechanical problems; difficult intubation; delayed intubation; failed intubation; cyanosis and cardiovascular collaspe [4–6, 10–12]. The hazards and difficulties of an awake rigid intubation include: any condition which results in a lack of rapport between the patient and anaesthetist; discomfort for the patient; aspiration because of either topical anaesthesia applied to larynx or heavy sedation [2, 7, 8, 10, 13, 14].

Awake tracheal intubation using a flexible fibreoptic endoscope should be a valuable alternative, because it increases the frequency of success if the intubation proves to be difficult [15–17], and minimizes the trauma and discomfort [16–18], and cardiovascular responses [19–20] associated with rigid laryngoscopy. In addition, awake fibreoptic laryngoscopy also appears to have a higher success rate than awake rigid laryngoscopy, even in patients who are not judged to present potentially difficult intubation [20]. As there do not appear to be any carefully documented reports describing the use of this technique for such patients, this descriptive report summarizes our experience with 129 awake fibreoptic tracheal intubations in 121 patients considered to be at high risk of aspiration of gastric contents.

PATIENTS AND METHODS

During a 6-yr period, two women and 121 men (mean age 60 (SD 12) yr; 78 (20) kg) considered at high risk of aspiration of gastric contents, underwent tracheal intubation with a flexible fibreoptic bronchoscope or laryngoscope (fibrescope) on 129 occasions, while awake (table I). All fibreoptic intubations performed on such patients during

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This article is accompanied by Editorial I.

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TABLE I. *Categories of patients at high risk of aspiration of gastric contents*

Category	No.
Emergency	
Acute abdomen	36
Miscellaneous operations (non-abdominal)	22
Small/large bowel obstruction	15
Upper gastrointestinal bleeding	10
Ludwig's angina/peritonsillar abscess	6
Non-emergency	
Presence of hiatus hernia	28
Intermittent bowel obstruction	7
Gastric outlet obstruction	3
Oesophageal diverticulum	2
Total	129

TABLE II. *Patients at high risk for aspiration also considered to present a difficult tracheal intubation*

Category	No.
Anticipated difficult intubation	
Ludwig's angina	6
Cervical and temporomandibular arthritis	5
Morbid obesity	3
Features such as a short thick neck, protruding upper incisors, large tongue or narrow mouth opening	5
Failed intubation with rigid larynoscope or by blind nasal approach	3
Known previous difficult intubation	3
Total	25

this period are included. The technique was used in 25 patients because of pathophysiological conditions which suggested that intubation would be difficult (table II); in the other patients it was chosen as the personal preference of the anaesthetist. All patients were interviewed before operation and verbal consent obtained. The patients were ASA physical status I or II (33 occasions), III (69 occasions), and IV (27 occasions). There were 39 nasal and 90 oral intubations. On 43 occasions premedication comprised diazepam 5–10 mg by mouth, or morphine sulphate 5–10 mg i.m., or both, in addition to atropine 0.4 mg i.m.; on 38 occasions the patients received only atropine, and on 48 occasions no premedication was given.

After insertion of a venous cannula and application of appropriate monitors, i.v. sedation was administered until the patient fell into a light sleep if unstimulated, but was still responsive to command and able to carry out instructions that might be given. On six occasions no sedation was used. The other patients received either a combination of diazepam 0.07 (0.03) mg kg^{-1} and fentanyl 1.7 (0.9) μg kg^{-1} ($n = 87$), or fentanyl ($n = 33$) or diazepam alone ($n = 3$), depending on age, general physical and medical status, condition of the airway, and any current use of drugs or alcohol. No local anaesthesia was used on 15 occasions, while on 29 occasions 4% lignocaine 3 ml was injected through the cricothyroid membrane. On the remaining 85 occasions, 4% lignocaine 4 ml was sprayed through the working channel of the fibrescope as described below.

For orotracheal intubation the mucus membranes of the mouth and pharynx were anaesthetized with five short sprays of benzocaine–amethocaine (Cetacaine) followed by application of benzocaine (Americaine) ointment to the base of the tongue. The intubating airway was inserted and the tracheal tube positioned in it. For nasotracheal intubation the nasal mucosa was anaesthetized by topical application of 4% cocaine, and the tracheal tube inserted through the nostril into the nasopharynx. In both circumstances the fibrescope was introduced through the tracheal tube and advanced until the vocal cords were identified. The fibrescope was passed into the trachea and the tracheal tube passed over it without delay when either no or transtracheal local anaesthetic had been applied. On the remaining 85 occasions the larynx was sprayed first with 4% lignocaine 2 ml through the working channel of the fibrescope, the tip of the fibrescope was advanced into the trachea 30 s later followed by a second spray of 4% lignocaine 2 ml to the trachea, and the tracheal tube was passed immediately into the trachea.

In all patients, gross evidence of aspiration of gastric contents into the trachea was sought through the fibrescope while it was withdrawn. Any complication encountered during intubation and the success or failure of the attempt were recorded. All patients were interviewed and examined after operation. Data obtained included symptoms or signs of aspiration in the immediate postoperative period (dyspnoea, respiratory distress, cyanosis, fever, tachypnoea, diffuse râles, bronchospasm and gross evidence of airway obstruction or atelectasis on physical examination), and radiological evidence of aspiration pneumonitis within 24 h of the operation. In the absence of such evidence, the patients were considered not to have suffered clinically significant aspiration. Clinical and radiological evidence of any other pulmonary complication during the postoperative period was also sought.

RESULTS

Fibreoptic intubation was successful in 128 of the 129 attempts, with no evidence of regurgitation or aspiration during any of the procedures. The only failure was in a 77-yr-old male (with a bleeding peptic ulcer) who vomited a large amount of fresh and clotted blood, during attempted nasotracheal intubation, and this obscured vision through the fibrescope. A rigid laryngoscope was used to complete the intubation. The only patient in whom two attempts with the fibrescope were required was a 68-yr-old male with a small bowel obstruction who developed laryngospasm and coughing, and vomited liquid material during attempted orotracheal intubation without laryngotracheal topical anaesthesia. The fibrescope was removed, the oropharynx cleared and, on re-insertion of the fibrescope, the vocal cords were seen and sprayed with 4% lignocaine 2 ml; 45 s later the fibrescope and then the tracheal tube were advanced successfully into the trachea. None of these two patients exhibited immediate symptoms or signs of aspiration and there were no pulmonary complications detected after operation. Six patients who underwent major intra-abdominal operations developed postoperative pulmonary complications: two had pleural effusions, one atelectasis and three infiltrates in the lungs. All complications developed after the first day after operation and none was thought to have resulted from aspiration.

Complications occuring during intubation included laryngospasm on 10 occasions and moderate to severe coughing on 32; two patients were oversedated with fentanyl 200 µg and diazepam 5 mg, and with fentanyl 50 µg and diazepam 5 mg, requiring verbal encouragement to breathe. No patient became apnoeic or developed airway obstruction as a result of sedation.

One hundred and four postoperative interviews were conducted. On 37 occasions the patients recollected the procedure, but on only three occasions did the patient consider the recollection unpleasant: one patient had undergone an attempted blind awake nasotracheal intubation followed by an attempted nasotracheal intubation using a rigid laryngoscope, before undergoing successful intubation with the fibrescope; the second patient had undergone a nasotracheal, and the third an orotracheal fibreoptic intubation, but because both had compromised airways neither had been given premedication, and one had received no i.v. sedation.

DISCUSSION

This study has documented the feasibility and safety of awake fibreoptic tracheal intubation in patients at high risk of aspiration, as an alternative to the two generally accepted techniques—rapid sequence induction and tracheal intubation, and awake tracheal intubation with a rigid laryngoscope [2, 4]. We believe this to be the first new method for dealing with this special circumstance since the rapid sequence induction and tracheal intubation with preoxygenation and cricoid pressure was described by Sellick in 1961 [1].

The primary advantages of fibreoptic intubation are its undoubted value in the management of a known or potential difficult tracheal intubation [15–17], and the lesser degree of hypertension and tachycardia that accompany it [19, 20]. Its initial use in our practice for patients at high risk of aspiration was for those patients who also presented a potentially difficult intubation. As experience was gained it began to be used as an additional approach for securing the airway in any patient at high risk of aspiration. It has three additional significant advantages over the rapid sequence induction and intubation technique: it is not subject to the three hazards of failure of cricoid pressure to prevent regurgitation and aspiration [12, 21], failure to intubate the trachea of such a patient [6, 10, 11], and cardiovascular collapse [10]. It has two advantages over awake rigid intubation in that it is less painful and unpleasant for the patient [2, 7, 8, 16–18], and it may have a higher success rate [20]. However, it has the disadvantage, compared with the rapid sequence induction and intubation technique, of recall of the intubation in many instances [17, 18].

Local anaesthesia of the larynx during fibreoptic or rigid intubation of an awake patient at high risk for aspiration is controversial [7, 8, 13]. Vandam included topical anaesthesia as part of the awake intubation technique, but warned that the larynx could no longer be assumed to be "awake" [2]. Walts recommended that only the base of the tongue, vallecula and epiglottis be anaesthetized, and that spraying local anaesthetic solution directly on the vocal cords, transtracheal anaesthesia and superior laryngeal nerve block should be avoided in patients at high risk of aspiration [7]. Thomas recommended that, although local anaesthetic sprayed directly on the larynx, and superior laryngeal nerve block could be used, transtracheal anaesthesia should be omitted, as the cough reflex would no longer be preserved [8]. In this study the cords were sprayed through the working channel of the fibrescope on 85 occasions and transtracheal anaesthesia was used on 29 occasions without any evidence of aspiration. Kopriva, Eltringham and Siebert [14] have shown in a small group of patients that, although local anaesthesia of only the tongue, vallecula and the lingual surface of the epiglottis did not result in incompetence of the largyeal closure reflex, laryngeal exposure with a rigid laryngoscope was successful in only 12 of 18 unsedated patients. In contrast, all of a second group of 12 patients who were sedated with Innovar 4–8 ml, but given no local anaesthesia, underwent successful intubation with a rigid laryngoscope, but evidence of incompetence of the laryngeal closure reflex was present in four of the patients [14].

We believe that the efficacy and safety of the fibreoptic technique can be maximized by the use of minimal or no sedation, the administration of oxygen during the intubation by nasal cannula if indicated, and the application of local anaesthetic to the larynx and trachea by spraying through the working channel of the fibrescope. If topical anaesthesia is applied when the tip of the fibrescope is in close proximity to the vocal cords, the fibrescope can be advanced into the trachea 30 s later and a second application sprayed into the trachea before the tracheal tube is advanced over the fibrescope. This technique appears to reduce the patient's discomfort and reaction to intubation, while minimizing the time during which the airway is unprotected.

The use of the fibrescope as reported in this study provides anaesthetists with a third option for securing the airway in patients at high risk of aspiration. Evaluation of its role compared with rapid sequence induction and intubation and awake rigid intubation awaits the completion of carefully controlled comparative studies.

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IN VIVO ASSESSMENT OF PERCUTANEOUS LOCAL ANAESTHETIC PREPARATIONS

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Recently, there has been increased interest in the application of percutaneous local anaesthesia for painfree venepuncture, particularly in children. It has been demonstrated that children in hospital undergoing venepuncture or catheterization often experience stress which results in making such comparatively minor procedures difficult both for the patient and the physican [1]. Topical anaesthetic preparations currently available, with the exception of Eutectic Mixture of Local Anaesthetics (EMLA) [2] provide only trivial surface anaesthesia. The ideal percutaneous local anaesthetic formulation should have a comparatively low concentration of drug and provide a rapid onset of action combined with a deep and relatively prolonged anaesthesia of the skin surface, in addition to underlying tissues [3–6].

Although EMLA has been available for some time, it requires a minimum application period of 1 h using 2.5 g of the preparation in combination with an occlusive dressing [7]. Furthermore, it has been reported that the anaesthetic effect remains for only approximately 30 min [8]. Previous studies have indicated that amethocaine would appear to be a more appropriate drug upon which to base a percutaneous local anaesthetic formulation [9, 10]. The present study has examined the percutaneous anaesthetic effect, in terms of both onset and duration, of a novel drug formulation based on amethocaine, compared with EMLA.

SUMMARY

This study has demonstrated greater efficacy of a new percutaneous amethocaine preparation relative to Eutectic Mixture of Local Anaesthetics (EMLA). Initially, a double-blinded trial was undertaken on each preparation individually against placebo, as the recommended method of application was different for EMLA (2.5 g applied for 60 min under an occlusive dressing) and the amethocaine formulation (0.5 g applied for 30 min). Thereafter, the two preparations were compared directly, in a double-blinded study using a standardized application for both formulations. The results indicated that both preparations provided significant (chi-square; $P < 0.001$) percutaneous local anaesthesia when compared with placebo. The amethocaine preparation produced significant anaesthesia (chi-square, $P < 0.001$) after 30 min application. Furthermore, the amethocaine formulation demonstrated both increased rapidity of action and increased duration of effect, as determined by a two-tailed unpaired t *test, in comparison with EMLA when application times of both 30 and 60 min were used for each preparation. The results of this study indicate that the amethocaine preparation provided more rapid and prolonged anaesthesia than EMLA.*

METHODS

Chemicals

Amethocaine base U.S.P. was obtained from Ward Blenkinsop Ltd, Cheshire, U.K. EMLA was obtained from Astra Pharmaceuticals Ltd, Hertfordshire, U.K.

Formulations

The amethocaine formulation was prepared as described previously [11] by dispersing ametho-

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caine (4% w/w) in carbomer (1.5% w/w) and filled into 25-g lacquered tubes using conventional pharmaceutical techniques. EMLA was repacked similarly from its original containers.

Volunteer studies

These studies were undertaken on 20 healthy volunteers (11 male), age range 18–47 yr, who each gave written informed consent. The study was approved by the local Ethics Committee. Each volunteer received all formulations. Both left and right forearms (ventral surface at or below the anterior cubital fossa) were used and a minimum period of 7 days was maintained between successive applications on previously treated individuals. Formulations were allocated to volunteers on a random basis.

Initially, both EMLA and the amethocaine formulation were assessed *in vivo* against a placebo using a double-blinded procedure [9]. In each case, the recommended procedure was followed. Thus EMLA was applied as 2.5 g per site under an occlusive dressing (Tegaderm, 3M) for 60 min, whereas the amethocaine formulation was used at 0.5 g per site under Op-Site I.V. (Smith and Nephew Ltd) for 30 min. Both preparations were removed following their respective contact times, the sites wiped clean and anaesthesia assessed by pinprick as described previously [9, 11].

Thereafter, a procedure was designed to compare directly the anaesthetic effect of the two formulations in a double-blind manner. All preparations were applied as 2.5 g per site under Tegaderm. Initially, the two active and two placebo formulations were applied, for a 30-min period, to each volunteer. After a minimum period of 7 days the two active and two placebo formulations were reapplied for a 60-min period.

Throughout the study, volunteers were asked to distinguish between full anaesthesia (coded 1) and no or partial anaesthesia (coded 0) as described previously [11].

Statistical analysis

Each preparation was analysed initially for efficacy directly against placebo (table I) using the chi-square test. Thereafter, both preparations were compared directly, using the standard procedure, in terms of efficacy (chi-square) and, where possible, both duration and onset of effect (two-tailed unpaired *t* test) (tables II and III).

TABLE I. *EMLA and the amethocaine formulation were assessed* in vivo *against placebo using the appropriate application procedure for each preparation. No volunteer exhibited an anaesthetic effect from placebo*

	EMLA		Amethocaine formulation	
Volunteer No.	Onset of anaesthesia (min)	Duration of anaesthesia (h)	Onset of anaesthesia (min)	Duration of anaesthesia (h)
1	60	1.0	40	3.0
2	70	0.5	45	4.0
3	60	0.5	30	3.5
4	75	1.5	35	2.5
5	60	1.0	30	5.0
6	80	1.5	45	4.0
7	—	—	40	3.0
8	60	2.0	35	5.5
9	70	0.5	40	2.5
10	65	1.0	35	4.0
11	60	1.5	30	3.0
12	60	0.5	35	4.0
13	90	0.5	40	7.0
14	60	2.0	45	3.0
15	75	1.0	30	5.0
16	60	0.5	35	2.5
17	70	0.5	30	4.0
18	60	1.0	40	3.5
19	85	0.5	40	5.0
20	60	1.5	30	3.0

TABLE II. In vivo *assessment of EMLA compared with the amethocaine formulation using a 30-min application period. No volunteer exhibited any anaesthetic effect from placebo*

	EMLA		Amethocaine formulation	
Volunteer No.	Onset of anaesthesia (min)	Duration of anaesthesia (h)	Onset of anaesthesia (min)	Duration of anaesthesia (h)
1	—	—	30	3.0
2	—	—	35	3.0
3	—	—	30	3.5
4	—	—	40	4.5
5	30	0.1	30	5.0
6	—	—	35	3.5
7	—	—	35	3.5
8	—	—	40	5.0
9	—	—	35	3.0
10	—	—	40	5.0
11	50	0.1	40	2.5
12	—	—	30	4.0
13	—	—	35	3.5
14	—	—	35	3.0
15	—	—	35	6.0
16	60	0.1	40	5.5
17	—	—	30	4.5
18	—	—	35	3.5
19	70	0.1	30	5.0
20	—	—	30	6.0

RESULTS

EMLA provided a 95 % success rate, while the amethocaine formulation provided anaesthesia in all subjects, both effects being significant compared with placebo ($P < 0.001$). The mean time for onset of anaesthesia was 67.4 (SD 9.6) min for EMLA and 34.5 (9.7) min for the amethocaine preparation. The effects lasted respectively for a mean of 1 (0.5) h and 3.8 (1.17) h (table I).

The two formulations exhibited different trends when applied for 30 min in the comparative double-blind study. The amethocaine formulation provided complete percutaneous local anaesthesia in all subjects, whereas EMLA was only 20 % successful, the duration of the effect being transient (table II). Under these conditions the amethocaine preparation was significantly more effective than EMLA (chi-square, $P < 0.001$). When both preparations were compared (table III) using a 60-min application time for each, both were significantly effective ($P < 0.001$ in each case). However, the amethocaine preparation (mean duration 4.5 (1.8) h) exhibited significantly longer duration of action ($P < 0.001$) than EMLA (duration 1 (0.5) h). Additionally, all volunteers were anaesthetized on removal of the amethocaine preparation at 60 min, whereas 55 % of volunteers required additional time for onset of effect following application of EMLA.

DISCUSSION

The different application regimens in respect of both the recommended application times and applied doses for EMLA and the amethocaine preparation presented some difficulties in the design of a suitable double-blinded trial. Therefore, it was decided initially to examine the anaesthetic formulations separately against placebo, using the recommended regimen for each preparation (table I). Both preparations provided significant percutaneous local anaesthesia when compared with placebo. However, it is clear from our data that the amethocaine formulation, with an application time 50 % that of EMLA, provided more rapid and prolonged anaesthesia than EMLA (table I), and therefore a double-blinded clinical trial was designed in order to compare the two preparations directly in terms of efficacy, rapidity and duration of anaesthesia.

In order to reduce the number of potential variables within the trial it was necessary to

TABLE III. In vivo *assessment of EMLA compared with the amethocaine formulation using a 60-min application period. No volunteer exhibited an anaesthetic effect from placebo*

	EMLA		Amethocaine formulation	
Volunteer No.	Onset of anaesthesia (min)	Duration of anaesthesia (h)	Onset of anaesthesia (min)	Duration of anaesthesia (h)
1	60	1.0	60	5.0
2	60	0.5	60	6.0
3	70	1.5	60	4.0
4	80	1.0	60	4.5
5	60	1.0	60	3.5
6	80	0.5	60	4.0
7	60	0.5	60	5.0
8	60	2.0	60	6.5
9	75	0.5	60	8.0
10	85	2.0	60	6 0
11	60	1.5	60	4.0
12	—	—	60	3.0
13	65	0.5	60	5.0
14	70	1.0	60	4.0
15	60	0.5	60	4.0
16	60	0.5	60	2.5
17	70	0.5	60	4.0
18	60	1.5	60	3.5
19	75	0.5	60	7.0
20	70	1.5	60	6.0

standardize both the amount of anaesthetic applied (2.5 g) and the dressing used (Tegaderm) for both preparations. This is the recommended regimen for EMLA, which requires both the occlusive dressing and a large applied dose for efficacy. Both 30-min (table II) and 60-min (table III) application times were used for each preparation. It is clear from our data that a 30-min application time for EMLA was insufficient to provide either adequate anaesthesia to pinprick or satisfactory duration of action. Only 20% of volunteers reported any anaesthetic effect under these conditions. The effect was transient, lasting only approximately 6 min. In contrast, the amethocaine formulation anaesthetized all volunteers to pinprick under these conditions, with a prolonged duration of effect. The poor efficacy of EMLA with this shortened application time is in agreement with a previous observation [7]. When a 60-min application time was used both preparations were effective. However, the amethocaine preparation had a significantly longer mean duration of action (4.5 h) than EMLA (1 h). Nevertheless, it is interesting to note that EMLA performed better in this trial with respect to duration of effect than has been reported previously [8], and that the mean duration of effect from the amethocaine preparation increased from 3.8 to 4.5 h when the application time was increased from 30 to 60 min.

The greater efficacy of the amethocaine preparation compared with EMLA, in terms of both quicker onset and prolonged action times, can be explained in terms of differences in lipophilicity and anaesthetic potency between amethocaine and the lignocaine–prilocaine eutectic mixture. Amethocaine is considerably more lipophilic than either of the two active constituents of EMLA [12]; the order of lipophilicity, and therefore anaesthetic potency, is amethocaine > lignocaine > prilocaine [13]. This implies that amethocaine would be expected to penetrate more easily and rapidly through lipophilic materials such as the stratum corneum [13]. It has been demonstrated previously that, when equimolar concentrations of amethocaine and lignocaine (in the same formulated system) were applied for a 30-min period to volunteers, the former drug provided a more significant percutaneous anaesthetic effect [9]. Therefore, not only is it likely that amethocaine may penetrate the stratum corneum more efficiently but, once the drug has reached the nociceptors in the viable dermis, it may produce satisfactory anaesthesia more easily, as the compound is considerably more potent than either lignocaine or prilocaine, the latter in particular having both low lipophilicity and low potency [13]. The greater affinity of the lipophilic amethocaine molecule for the stratum corneum may result in a depot effect in which the drug is retained for some period in the skin barrier.

It is evident from our data that the amethocaine formulation provided a more prolonged percutaneous anaesthetic activity in comparison with EMLA (tables I and III). Because of the potency of the drug, only comparatively small amounts need to be present in the environment of the nociceptors to exert a pharmacological action. Therefore, it is probable that a relatively long time would be required to reduce the concentration of amethocaine present at the nociceptors to less than that necessary for anaesthetic effect. Some confirmation of this suggestion may be implied by analysis of the data in table III: when the amethocaine formulation was applied for 60 min, the duration of anaesthesia was more prolonged than for the 30-min application. Clearly, more drug would be absorbed during the longer application time and it would be reasonable to suggest that, because of this, drug clearance would be prolonged. A similar overall effect may be seen for EMLA: a 30-min application period was inadequate to permit sufficient lignocaine–prilocaine (less lipophilic than amethocaine) to penetrate the stratum corneum to achieve an anaesthetic effect.

There were no untoward reactions to either preparation. EMLA sometimes produced a slight blanching effect on the skin. In contrast, the amethocaine preparation occasionally produced a slight transient erythema because of the vasodilator effect of the drug. Even when comparatively large amounts of the amethocaine preparation have been used, as for the painfree cutting of split skin grafts [10], no adverse effects were noted with the amethocaine preparation. A combination of drug retention in, and consequent slow release from, the stratum corneum, together with the action of non-specific esterases in the skin, probably accounts for the lack of any systemic toxicity associated with the use of this novel formulation.

From a clinical viewpoint there may be a considerable advantage, under certain circumstances, in using a percutaneous local anaesthetic preparation possessing a prolonged activity. For example, in taking split-skin grafts a prolonged anaesthetic action may considerably reduce postoperative pain [10]. Furthermore, the amethocaine formulation has a demonstrably shorter onset time than EMLA, with consequent advantages for both ward routine and potential outpatient clinical usage.

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STUDIES ON MORPHINE DISPOSITION: INFLUENCE OF GENERAL ANAESTHESIA ON PLASMA CONCENTRATIONS OF MORPHINE AND ITS METABOLITES†

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SUMMARY

The kinetics of morphine were studied during balanced anaesthesia in 10 patients undergoing lower abdominal or body surface surgery, and compared with those obtained in nine awake patients receiving morphine i.v. for the relief of chronic non-cancer pain. All patients received morphine sulphate pentahydrate 10 mg i.v. over 30 s. Venous blood samples were collected for up to 180 min, and plasma concentrations of morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) assayed by a differential radioimmunoassay technique. There were no differences between groups with respect to the elimination half-life (awake group: 207 min; anaesthetized group: 153 min), volume of distribution at steady state (awake: 147 litre; anaesthetized: 128 litre), or clearance (awake: 587 ml min^{-1}; anaesthetized: 766 ml min^{-1}). Peak concentrations of M3G were similar in the two groups, but the peak concentration of M6G was greater in the anaesthetized patients. The AUC for M3G and M6G (0–180 min) also were greater in the anaesthetized patients, presumably as a result of decreases in renal blood flow and glomerular filtration rate during halothane anaesthesia.

General anaesthesia and surgery cause alterations in hepatic and renal blood flow when compared with the awake patient. Anaesthesia may also cause changes in peripheral blood flow distribution. Thus anaesthesia may influence perioperative drug disposition by three separate effects: on drug distribution, on hepatic blood flow and on drug elimination. Tranquilli and colleagues [1] have shown nitrous oxide–halothane anaesthesia in swine caused changes in peripheral blood flow, especially within the splanchnic circulation, fatty tissues, skeletal muscle and skin. Furthermore, general anaesthesia also causes reduction in renal blood flow, and hence a decrease in the glomerular filtration rate. Thus elimination of drug metabolites may also be affected by general anaesthesia.

Morphine is metabolized principally in man by biotransformation to two glucuronides which are eliminated by renal filtration. Morphine-3-glucuronide (M3G) is pharmacologically inactive, while morphine-6-glucuronide (M6G) has been shown to be analgesically active when injected intracerebrally and subcutaneously in mice [2]. M6G is known to enter the central nervous system in man after single doses of morphine 10 mg [3]. There is also growing evidence to suggest that increased plasma concentrations of M6G in man may account for the increased efficacy of the opioid when given to patients with impaired renal function.

There are no studies to date investigating the influence of general anaesthesia on morphine and its metabolites in man. The present study has compared, therefore, the disposition of the parent compound and its two main metabolites in two groups of patients: one awake and receiving the opioid for relief of chronic non-cancer pain; the second receiving morphine as part of balanced anaesthesia for lower abdominal or body surface surgery.

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PATIENTS AND METHODS

Nineteen patients (ASA I or II, aged 36–60 yr, weights 50.3–89.4 kg) were studied after giving their informed consent to participation in the programme, which was approved by the local hospital Ethics Committee.

Nine patients undergoing treatment for chronic non-cancer pain received morphine sulphate pentahydrate (Evans Medical, Beaconsfield, Bucks) 10 mg given i.v. over 30s in 10 ml of normal saline (0.154 mol litre^{-1}). None of these patients was receiving other drugs known to alter hepatic blood flow or hepatic metabolizing enzyme ability; none had previously received morphine or other opioids.

The other 10 patients were undergoing lower abdominal or body surface surgery. Premedication comprised diazepam 10–15 mg by mouth, 90 min before induction of anaesthesia with a sleep dose of thiopentone 4–5 mg kg^{-1}; the trachea was intubated following neuromuscular blockade with alcuronium 0.25 mg kg^{-1}. Anaesthesia was maintained with 67 % nitrous oxide in oxygen supplemented by halothane (up to 1 %). When stable haemodynamics had been achieved after induction, morphine sulphate pentahydrate 10 mg was given i.v. over 30 s. At the end of surgery, residual neuromuscular blockade was antagonized with atropine and neostigmine. In both study groups, arterial pressure and heart rate were monitored continuously, as was the electrocardiogram in those patients undergoing surgery.

Venous blood samples (2 ml) were collected from a cannula in the arm contralateral to the site of drug administration before injection of morphine and at 1, 2, 5, 7, 10, 15, 30, 45, 60, 90, 120, 150 and 180 min after injection. Samples were taken into lithium–heparin tubes and the plasma separated by centrifugation and stored at −20 °C until assayed for morphine and the two metabolites by a differential radioimmunoassay technique described by Hand and colleagues [4]. The assay for morphine has a coefficient of variation of 5–10 % over the concentration range reported here, a sensitivity of 10 nmol litre^{-1}; and cross reactivity with M3G, M6G and normorphine of 0.07 %, 0.1 % and 0.02 %, respectively.

Kinetic parameters were calculated using model-independent methods. The areas under the concentration–time curve ($\text{AUC}_{0\text{–}180}$) for morphine, M3G and M6G were determined using the linear trapezoidal rule. The extrapolated $\text{AUC}_{180\text{–}\infty}$ for morphine was calculated from the concentration at 180 min and the elimination rate constant. Other kinetic parameters for morphine (systemic clearance (Cl_P); apparent volume of distribution during the elimination phase (Vd^{area}); volume of distribution at steady state (Vd^{ss}); mean residence time (MRT)) were determined from the AUC and its first moment, AUMC.

Plasma concentration data and AUC for morphine, M3G and M6G were compared between the two groups using the Mann–Whitney *U* test, as were the derived kinetic parameters. Data are expressed throughout as the mean (SD), and range.

RESULTS

The patients in the two study groups were comparable for age and weight. The duration of anaesthesia was 91.8 (19.9) min. During anaes-

TABLE I. *Plasma morphine concentrations (nmol litre^{-1}) in awake and anaesthetized patients receiving morphine sulphate pentahydrate 10 mg i.v. Data shown as mean (SD) [range]*

Time (min)	Awake ($n = 9$)	Anaesthetized ($n = 10$)
1	2436 (2130) [537–5555]	2777 (1029) [1948–4248]
2	1092 (907) [463–3146]	1429 (328) [883–1919]
5	357 (120) [150–572]	427 (116) [347–574]
7	261 (58) [174–357]	310 (66) [224–423]
10	227 (50) [147–283]	275 (61) [171–392]
15	168 (50) [130–289]	199 (36) [147–246]
30	147 (26) [113–181]	128 (35) [96–184]
45	146 (46) [99–235]	102 (16) [79–124]
60	114 (20) [84–145]	95.3 (21) [63.2–134]
90	99 (30) [58–149]	79.9 (19) [48.9–108]
120	86.5 (14) [66–111]	70.9 (20) [50–115]
150	91.7 (29) [55–144]	72.7 (31) [44–130]
180	80.7 (27) [55–142]	53.5 (18) [32–85]

TABLE II. *Derived kinetic parameters for morphine, and concentration–time data for morphine-3-glucuronide and morphine-6-glucuronide in awake and anaesthetized patients. Data shown as mean* (*SD*) [*range*]. $^*P < 0.05$; $^{**}P < 0.025$; $^{***}P < 0.006$

	Awake patients		Anaesthetized patients
Elimination half-life (min)	207.7 (73.8) [112.1–318.3]		153.1 (60.6) [79.1–270.8]
MRT (min)	274.0 (110.5) [154.7–429.0]		189.4 (93.0) [85.1–318.1]
Cl_p (ml min^{-1})	587.3 (192.3) [289.2–955.5]		766.1 (212.2) [406.5–1121.1]
Vd^{ss} (litre)	146.8 (38.6) [98.6–205.7]		128.1 (31 6) [54.8–166.8]
Vd^{area} (litre)	161.1 (40.2) [126 6–235.6]		157.2 (42.1) [87.9–212.3]
Morphine-3-glucuronide			
C_{max} (nmol litre^{-1})	568 (189) [232–797]		694 (213) [489–1236]
T_{max} (min)	59 (46) [20–150]		51 (30) [30–120]
AUC (nmol litre^{-1} min)	69295 (26184) [29496–105904]	***	104486 (24417) [76296–159230]
Morphine-6-glucuronide			
C_{max} (nmol litre^{-1})	64.4 (33.0) [11.5–103.7]	*	102.4 (44.4) [54.5–181.4]
T_{max} (min)	51 (33) [5–120]		53 (19) [30–90]
AUC (nmol litre^{-1} min)	7114 (4128) [1679–12932]	**	13207 (6306) [6805–26344]

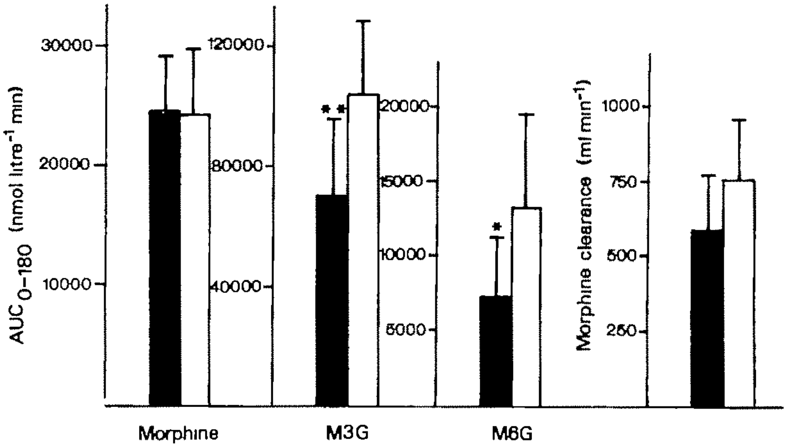

FIG. 1. Area under concentration–time curves from 0 to 180 min for morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), and morphine clearance in awake patients (black columns) and anaesthetized patients receiving morphine sulphate pentahydrate 10 mg i.v. Data shown as mean and SD. $^*P = 0.025$; $^{**}P = 0.006$ (Mann–Whitney U test).

thesia, heart rate and arterial pressure remained within 15–20% of pre-induction values.

Plasma morphine concentrations decayed in a curvilinear fashion in both groups (table I). The AUC_{0-180} for morphine was 24646 (4674) nmol litre^{-1} min for the awake patients and 24253 (5430) nmol litre^{-1} min for the anaesthetized group (no significant difference (ns)). Systemic morphine clearances calculated as dose/$AUC_{0-\infty}$ were 587 (192) ml min^{-1} and 766 (212) ml min^{-1} in the awake and anaesthetized patients, respectively (ns) (table II). The elimination half-lives, Vd^{area}, Vd^{ss} and MRT for morphine were similar for the two patient groups.

However, there were differences between the groups with respect to the time to peak concentration (T_{max}) and the peak concentration (C_{max}) for the two glucuronides in addition to the AUC_{0-180} for M3G and M6G (fig. 1). The AUC_{0-180} for M3G in awake subjects was 69295 (26184) nmol litre^{-1} min, and 104486 (24417) nmol litre^{-1}min in the anaesthetized patients ($P = 0.006$). Similar differences were found for M6G: 7114 (4128) nmol litre^{-1} min in the awake patients, and 13207 (6306) nmol litre^{-1} min in the anaesthetized group ($P = 0.025$). C_{max} (M6G) was significantly greater in the anaesthetized patients ($P < 0.05$).

Anaesthesia increased the plasma M3G AUC to plasma morphine AUC ratio (0–180 min) from 2.9 (1.3) to 4.3 (0.6) ($P = 0.01$), but had no significant effect on the plasma M6G AUC to plasma morphine AUC ratio over the same period: 0.32 (0.21) and 0.54 (0.20), respectively.

DISCUSSION

Although many studies have described the influence of anaesthesia upon parent drug disposition, there are few where the authors have measured drug metabolites and investigated the effects of general anaesthesia upon their elimination.

In the absence of surgery, inhalation anaesthesia causes a decrease in cardiac output and liver blood flow [5, 6]. In addition, nitrous oxide also decreases splanchnic blood flow [7, 8]. In the presence of surgery, different authors have reported varying effects on hepatic blood flow. Surgical laparotomy usually resulted in decreased hepatic arterial blood flow [9–11]. Using radiolabelled colloidal gold, Gelman [12] showed greater decreases in liver blood flow during upper abdominal compared with lower abdominal or body surface surgery in patients receiving 0.5–1.0% halothane to supplement nitrous oxide in oxygen. However, if indocyanine green (ICG) clearance is used as an indirect index of hepatic blood flow, then data from Nancarrow and colleagues [13] and Cousins and colleagues [14] would suggest halothane anaesthesia in concentrations of 0.35–0.5% to supplement nitrous oxide in oxygen has little effect on liver blood flow. On the other hand, Gelman, Fowler and Smith [15] have demonstrated that ICG clearance decreased progressively with increasing doses of halothane. However, these results did not correlate with the observed measured flow changes, suggesting that the hepatic extraction ratio of ICG changed during halothane anaesthesia.

In the present study, general anaesthesia did not inhibit the elimination of morphine. This is in agreement with the data of Merrell and colleagues [16], who were unable to demonstrate any effect of halothane anaesthesia on the formation of M3G from morphine in dogs. Both Mather and colleagues [17] and Behne and colleagues [18] have also shown in sheep an absence of any significant effect of volatile anaesthetic agents on the clearance of lignocaine and midazolam, although this is in contrast to the findings of Bentley, Glass and Gandolfi in man [19]. In addition, there have been reports of significant decreases in systemic clearance of fentanyl, systemic and intrinsic clearance of propranolol and systemic clearance of verapamil during halothane anaesthesia in dogs [20–22].

Mean clearances of morphine in our anaesthetized and awake patient groups were comparable to those reported in the study of Aitkenhead and colleagues (11.5 ml kg^{-1} min^{-1}), in which a similar blood sampling procedure was adopted, but morphine concentrations were assayed by HPLC [23]. The elimination half-life in both patient groups was similar also to that obtained by Aitkenhead; in both studies the limited duration of sampling limited the accuracy of this half-life, tending to underestimate the true value. The large variability in morphine clearance and half-life in both the anaesthetized and awake patient groups may be related to a number of factors: patient age and sex, other intercurrent medication, renal function, etc. Similar dispersion of data may be seen in the patients studied by Aitkenhead [23], and the other studies he cited, and it is unlikely, therefore, that the variability in our patients may be explained solely on the basis of assay methodology.

Of greater interest than the unaltered elimination of morphine was the increased AUC for both M3G and M6G in the anaesthetized patients. There is a decrease in renal blood flow and glomerular filtration rate during halothane anaesthesia in man [24, 25; Groves and Rosen, European Academy of Anaesthesiology, Ghent] which, in the presence of normal hepatic drug metabolism, leads to increased plasma concentrations of renally excreted metabolites.

Published data [26] for the elimination half-life of M3G in healthy patients reveal values between 2.4 and 6.7 h and hence are in excess of the half-life of the parent compound in this study. The only estimate for the half-life of M6G is approximately 2 h following a single i.v. dose of M6G 1 mg/70 kg body weight [27]. The short sampling time in the present study has precluded an estimate of the half-life of these two metabolites in each patient group. However, the increased AUC for both in the anaesthetized patients suggests prolongation of the half-life and, hence, prolongation of any dynamic effects of an active metabolite. The percentage increase in AUC for M3G and M6G in the anaesthetized patients is approximately 80%; studies on the influence of anaesthesia on renal blood flow and hence the glomerular filtration rate suggest the latter decreases by a comparable extent (between 30 and 50%) [24, 25]. Other mechanisms for the increased AUC might involve reduced biliary excretion of the glucuronides, but the present study was not designed to answer this question.

Inspection of the data for M3G and M6G does not suggest any relationship between the duration of anaesthesia and the AUC_{0-180} for each glucuronide, or a relationship between the C_{max} or T_{max} for either M3G or M6G and duration of anaesthesia. Thus we cannot comment on whether or not the impaired elimination of the glucuronides was confined solely to the intraoperative period. However, Selby and colleagues [28], using a chronically cannulated sheep model, have shown a persistent effect of anaesthesia on renal function extending into the early postoperative period.

Morphine-6-glucuronide binds rapidly and avidly to opioid receptors in bovine brain, while its analgesic potency in rodents is greater than that of morphine after either subcutaneous or intracerebral injection [2, 29]. Pasternak and colleagues [30] have reported that M6G is a powerful mu agonist, with a binding affinity similar to that of the parent compound, but with a 20-fold increased potency. In addition, increased plasma concentrations of M6G in patients with renal failure may be one cause of the exaggerated opioid responses following morphine [31, 32]. It is not clear, in the healthy patient undergoing general anaesthesia, if the increased AUC for M6G (0–180 min) contributes to an enhanced analgesic effect for a given dose of morphine. However, the influence of general anaesthesia on morphine disposition may be a more significant factor in patients with pre-existing impaired renal function.

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STUDIES ON MORPHINE DISPOSITION: INFLUENCE OF RENAL FAILURE ON THE KINETICS OF MORPHINE AND ITS METABOLITES

J. W. SEAR, C. W. HAND, R. A. MOORE AND H. J. McQUAY

SUMMARY

The influence of renal failure on the disposition of morphine and its metabolites was studied in nine patients with end-stage renal failure undergoing transplantation, and compared with five healthy anaesthetized patients. All patients received morphine sulphate pentahydrate 10 mg i.v. over 30 s, as part of a balanced anaesthetic technique. Venous blood samples were collected for up to 24 h, and plasma concentrations of morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) assayed by a differential radioimmunoassay method. There were no differences between the two groups for morphine elimination half-life (renal failure: 290 min; anaesthetized controls: 286 min), or clearance (renal failure: 533 ml min^{-1}; controls 741 ml min^{-1}). However, the volume of distribution at steady state was greater in the control group (241 litre v. *141 litre;* $P = 0.002$*). The peak concentrations of M3G and M6G were greater in the renal transplant patients (*$P = 0.001$ *and* $P = 0.01$*, respectively), as were the AUC (0–24 h) (*$P = 0.002$ *and* $P = 0.002$*). M6G has been shown to possess analgesic properties in both man and experimental animals, and therefore the increased AUC for M6G may contribute to the prolonged effect seen with morphine when given to patients with impaired renal function.*

Prolonged and profound analgesia, sedation and ventilatory depression have been reported in patients suffering from renal failure and receiving parenteral doses of morphine [1–3]. Our previous studies suggested altered kinetics of morphine in anaesthetized patients receiving the opioid as part of a balanced anaesthetic technique for renal transplant surgery [4]. On the other hand, Aitkenhead and colleagues [5] and Woolner and colleagues [6] reported no alteration in parent drug disposition when i.v. morphine was administered to awake individuals with chronic renal failure. More recently, using a double radioimmunoassay technique, Chauvin and colleagues [7] reported unaltered morphine disposition in anaesthetized uraemic patients undergoing surgery for arterio–venous fistula formation. However, these authors did not assay the two glucuronides of morphine separately.

Criticisms and problems with many studies investigating the kinetics of morphine relate to assay methodology, and in particular to a lack of specificity of many radioimmunoassay antisera [8]. Recently, a differential radioimmunoassay technique has been reported that is specific for morphine, and also allows measurement of the two glucuronides of the opioid [9].

The present study has therefore re-investigated the pharmacokinetics of morphine both in healthy anaesthetized patients, and in patients with renal failure undergoing renal transplanation. The use of three separate antisera has allowed estimation of plasma concentrations of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G).

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PATIENTS AND METHODS

The disposition of morphine was investigated in 14 patients, who gave their informed consent to the studies which were approved by the local research Ethics Committee.

Nine patients (four female; ages 19–48 yr, weights 46.8–70 kg) were studied while undergoing renal transplantation. Concurrent medication, including antihypertensive and anti-anginal drugs, was continued up to the morning of surgery, and additional drugs were given with premedication where appropriate. All the patients had undergone haemodialysis within the previous 6–20 h.

Patients were premedicated with oral diazepam 10 mg given 2 h before anaesthesia. Sleep was induced with thiopentone 3–4 mg kg^{-1}, and the trachea intubated after neuromuscular blockade was produced with vecuronium 0.1 mg kg^{-1}. Anaesthesia was maintained with nitrous oxide in oxygen supplemented with enflurane (up to 0.8% inspired concentration).

Following the onset of stable anaesthesia, morphine sulphate pentahydrate 10 mg in normal saline 10 ml (morphine 26.4 μmol) was injected into a flowing peripheral infusion over 30 s. Venous samples (from a central venous catheter) were collected before induction of anaesthesia, at 1, 2, 5, 10, 15, 30, 45, 60, 90, 120, 180 min and at appropriate times to 1440 min after i.v. injection of morphine. Blood samples were collected into tubes containing lithium heparin, plasma separated by centrifugation, and stored at −20 °C until analysis. Samples were assayed for morphine and its two glucuronides using three separate antisera under optimum conditions [9].

During operation, patients received crystalloid infusions (sodium chloride 0.154 mol $litre^{-1}$ and 5% dextrose) and plasma substitutes (Haemaccel) to maintain a central venous pressure of 10–12 cm H_2O. Arterial pressure, heart rate and electrocardiogram were monitored continuously. Immunosuppression was provided by cyclosporin, azathioprine and hydrocortisone.

Data were obtained from five healthy anaesthetized patients (two female; ages 16–55 yr) undergoing elective surgery for ligation of a cerebral aneurysm following subarachnoid haemorrhage. All patients were normotensive at the time of surgery; intraoperative hypotension for application of the clip to the neck of the aneurysm did not exceed a systolic arterial pressure of 80 mm Hg. Premedication and anaesthetic management were similar to those detailed for the renal transplant patients. Morphine sulphate pentahydrate 10 mg was administered when stable anaesthesia had been achieved, and blood sampling was continued to 1440 min.

Data analysis

Kinetic parameters were calculated using a model-independent method. The terminal or elimination half-life was determined by non-linear regression analysis. The area under the concentration–time curve (AUC) and its first moment (AUMC) were derived using the linear trapezoidal method, and hence allowed calculation of the volume of distribution at steady state (Vd^{ss}), systemic clearance (Cl_P), and mean residence time (MRT).

Data within the two groups were compared using the Mann–Whitney *U* test. $P < 0.05$ was considered significant.

RESULTS

The conduct of anaesthesia was uneventful in all patients. Six of the transplant patients were receiving beta-adrenoceptor blocking drugs. The preoperative haemoglobin, plasma urea and creatinine concentrations in the transplant patients were in the ranges 5.8–10.9 g dl^{-1}, 9.0–33.9 mmol $litre^{-1}$ and 466–911 μmol $litre^{-1}$, respectively. Immediate postoperative creatinine clearances in the transplant patients were between 36 and 138 ml min^{-1}.

Plasma morphine concentrations declined in a curvilinear manner, with a terminal half-life between 204 and 350 min in the healthy patients (mean: 286 min), and 115 and 707 min (mean: 290 min) in the renal transplant patients (not significantly different). The derived kinetic parameters (Cl_P, MRT, Vd^{ss}) are shown for the two groups in table I.

However, there were differences in the peak concentration (C_{max}) and time to this peak (T_{max}) for the two glucuronide metabolites in the two patient groups (table II). Peak concentrations of M3G ranged between 243 and 447 nmol $litre^{-1}$ in the healthy patients with T_{max} between 30 and 90 min. In the recipients of renal transplants, C_{max} was 720–1243 nmol $litre^{-1}$ and T_{max} 60–240 min ($P = 0.001$ and 0.01, respectively). Similar differences existed for M6G, with peak concentrations of 21–112 nmol $litre^{-1}$ in the

TABLE I. *Derived kinetic parameters for morphine in healthy anaesthetized patients* (n = 5) *and patients undergoing renal transplantation* (n = 9). *Data shown as mean* (*SD*) [*range*]. **P = *0.002* (*Mann–Whitney* U *test*)

	Anaesthetized patients	Transplant patients
Elimination half-life (min)	286.0 (53.1) [203.7–350.0]	290.4 (191.1) [114.9–707.1]
Cl_p (ml min^{-1})	741.0 (169.0) [570.2–971.5]	533.0 (298.0) [225.4–925.5]
Vd^{ss} (litre)	240.8 (55.1) [195.4–334.9]	140.9 (37.8) [102.2–220.8]**
MRT (min)	326.6 (30.2) [326.6–351.4]	373.3 (264.5) [132.7–924.6]
AUC$_{0-24}$ (nmol litre^{-1} min)	37044 (7940) [27158–46271]	65631 (34462) [28509–117605]

TABLE II. *Concentration and time data for morphine-3-glucuronide and morphine-6-glucuronide in healthy anaesthetized patients and patients undergoing renal transplantation. Data shown as mean* (*SD*) [*range*]. *P < *0.02;* **P < *0.01;* ***P < *0.001* (*Mann–Whitney* U *test*)

	Anaesthetized patients		Transplant patients
Morphine-3-glucuronide			
C_{max} (nmol litre^{-1})	320.3 (79.0) [242.5–447]	***	964.4 (191.1) [720–1243]
T_{max} (min)	51.0 (25.1) [30–90]	**	137.8 (54.5) [60–240]
[AUC (nmol litre^{-1} min)	123322 (22480) [90380–146712]	***	695542 (181813) [404182–1026364]
Morphine-6-glucuronide			
C_{max} (nmol litre^{-1})	52.2 (40.6) [21.2–112.1]	*	126.5 (61.5) [50.3–252.4]
T_{max} (min)	108.0 (45.5) [60–180]		162.2 (47.4) [120–270]
[AUC (nmol litre^{-1} min)	15336 (7821) [8553–28296]	***	80206 (29867) [51773–117102]
Ratio C_{max} M3G: C_{max} M6G	10.2 (8.0)		8.7 (3.9)
AUC$_{0-24\,h}$ M6G: Morphine	0.43 (0.28)		1.78 (1.37)

healthy group, and 50–252 nmol litre^{-1} in the transplant patients ($P = 0.02$). There were no differences in the T_{max} ranges for M6G.

However, the AUC (0–1440 min) for M3G and M6G were significantly greater in those patients undergoing renal transplanation ($P < 0.001$) (table II, fig. 1). There was also a significantly greater value for the ratio AUC morphine-6-glucuronide/AUC morphine in the renal transplant patients ($P < 0.02$). In the nine patients with renal failure, there was no significant correlation ($r = 0.264$) between this ratio and immediate graft function expressed as the 24-h creatinine clearance.

The estimated half-lives in the transplant patients were 304–918 min for M3G and 217–898 min for M6G, compared with 173–324 min and 104–127 min in the healthy anaesthetized patients.

DISCUSSION

The disposition of morphine in renal failure patients undergoing transplantation was not significantly different from that in healthy anaesthetized patients, with the exception of a decrease in the volume of distribution at steady state (Vd^{ss}). This difference was observed also by Aitkenhead and colleagues in awake subjects [5], and by Chauvin and colleagues [7] in anaesthetized patients, in whom morphine concentrations were assayed by HPLC and RIA, respectively. A considerable variability in morphine kinetics in healthy anaesthetized patients has been reported [10–13]. This may relate to many factors such as study design, patient age and sex, anaesthetic technique, concurrent therapy, duration of sampling and assay methodology [14].

Comparing the mean data for healthy anaesthetized patients from the present study and those from Chauvin [7], the coefficients of variation for elimination half-life, clearance and apparent volume of distribution at steady state range between 20 and 30%, with no difference between the two studies. A similarly wide dispersion of data in both healthy and renal failure patients can be seen in the study of Aitkenhead and colleagues [5]. In the presence of renal failure, other factors may also interplay; these include a reduced total body water secondary to haemodialysis, and altered protein binding or plasma albumin concentrations.

Comparison of the data for healthy patients in

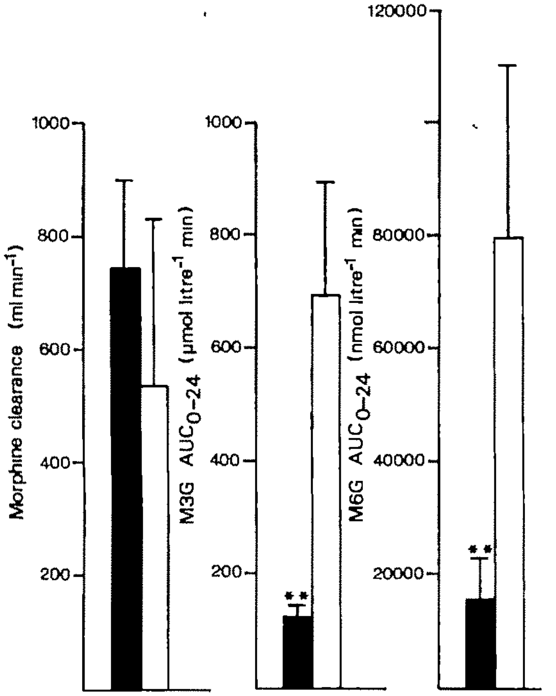

FIG. 1. Morphine clearance and area under concentration–time curves from 0–24 h for morphine, morphine-3-glucuronide and morphine-6-glucuronide following morphine 10 mg i.v. to healthy anaesthetized patients (black columns) ($n = 5$) and to patients undergoing renal transplantation ($n = 9$). Data shown as mean (SD). $^{**}P < 0.002$ (Mann–Whitney *U* test).

this study and those for the anaesthetized group in the accompanying publication [15] show a longer elimination half-life and greater volume of distribution. This may be explained by the short sampling period in the previous study (180 min compared with 24 h), leading to an underestimation of the terminal half-life.

Why do these results differ from our earlier data [4]? Studies of the specificity of the RIA used in that paper reported a 1 % molar cross reactivity of the antiserum to morphine-3-glucuronide (the principal metabolite of morphine) and a 0.3 % cross reactivity to normorphine [13]. Antisera produced by haptenization through 6-hemisuccinyl morphine also demonstrate significant cross reactivity to morphine-6-glucuronide. Boerner, Abbott and Roe [16] indicated a ratio of 100:1 for morphine-3-glucuronide to morphine-6-glucuronide in the urine of post-addict males. However, Svensson and colleagues have demonstrated greater concentrations of M6G—approximately 10 % of M3G during chronic oral medication with morphine [17]. This is also in agreement with our own data following i.v. administration [9]. Hence our earlier morphine kinetics in patients with renal failure were inaccurate because of simultaneous measurement of both morphine and morphine-6-glucuronide [4].

Other data showing increased concentrations of M3G and M6G in patients with chronic renal failure have been reported [3, 18], in addition to altered kinetics of M6G when given i.v. to patients with renal failure compared with healthy volunteers [19]. Both of the studies reporting the disposition of morphine and its metabolites in renal failure [3, 18] indicated half-lives for M3G of 14.5–136 h, and M6G 38–1[illegible]3 h. Compared with these other reports, the shorter half-lives in our transplanted group may reflect restoration towards normal renal function that occurs following revascularization of the grafted kidney.

Morphine-6-glucuronide has been shown to be analgesically active when administered intracerebrally to rats, and to exhibit avid binding to opioid receptors in bovine brain [20–23]. In a preliminary study in man, Osborne [19] has reported that 1 mg of M6G provided analgesia lasting for 1–7 h. The increased peak concentrations and AUC for M6G in the patients with renal failure may be important in causing the enhanced clinical effects attributed to the parent opioid. Although the glucuronide metabolites are more polar and less lipid soluble than the parent compound, and hence show only slow diffusion into CSF, plasma accumulation of M6G may allow its more rapid diffusion into central nervous tissue, leading to the classical picture of respiratory depression [2, 3].

This present study has confirmed that renal dysfunction does not impair the clearance of morphine in the anaesthetized patient, but does alter clearance of the glucuronide metabolites. The clinical importance of this may relate to the net effect of a single dose of morphine being the sum of the effects of the parent compound and its active metabolite(s). If this is the case, increased M6G concentrations may predispose to a greater net effect for any given dose of morphine.

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EFFECT OF HALOTHANE, ENFLURANE AND ISOFLURANE ON CAROTID BODY CHEMORECEPTOR ACTIVITY IN THE RABBIT AND THE CAT

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SUMMARY

The response of the carotid body chemoreceptors to administration of halothane, enflurane and isoflurane was tested in the rabbit and cat. In the steady-state all three volatile anaesthetics, in doses up to 1%, were mildly chemodepressant. The oxygen response curves were shifted downwards, but hypoxic stimuli below 5.3 kPa overcame this chemodepression. Two-point carbon dioxide response curves were also shifted downwards, but with no change in slope. Possible mechanisms involved in the chemoreceptor response to transient and steady-state anaesthetic administration are discussed.

The ventilatory response to hypoxia and hypercapnia is reduced by halothane, enflurane and isoflurane in humans [1–4] and dogs [5]. Part of this effect may result from direct depression of peripheral arterial chemoreceptor activity, as halothane reduces the carotid body chemoreceptor response to hypoxia and hypercapnia in cats [6, 7]. There are no equivalent data for enflurane and isoflurane, or studies on species other than the cat. The role of the carotid body chemoreceptors in this depression of ventilatory response was investigated, therefore, in the rabbit and cat by recording directly the hypoxic and hypercapnic responses of single chemoreceptor fibres before, during and after administration of the three halogenated anaesthetics.

METHODS

Anaesthesia and dissection

Investigations were performed in 12 New Zealand White rabbits (2.58–5.10 kg) and eight cats (2.30–3.70 kg). Anaesthesia was induced with pentobarbitone 40 mg kg^{-1} administered through an ear lobe vein in the rabbit and intraperitoneally (i.p.) in the cat. Anaesthesia was maintained with an infusion of pentobarbitone 4–6 mg kg^{-1} h^{-1} through a femoral vein. A femoral artery was cannulated for monitoring arterial pressure and for withdrawing blood for gas analysis (Corning 158).

Following tracheotomy and paralysis with pancuronium bromide (2-mg bolus followed by 0.05–0.08 mg kg^{-1} h^{-1}) the lungs were ventilated artificially. Gas mixtures of varied oxygen and carbon dioxide content were delivered to the ventilator via a system of rotameters. Volatile anaesthetics were added to the inspiratory gas mixtures by placing a Goldman vaporizer in series with the inspiratory port of the ventilator. Tracheal carbon dioxide, oxygen and end-tidal anaesthetic concentration were monitored continuously (Datex Normocap and Normac). Rectal temperature was maintained at 37 °C by means of a servo-controlled electric heating blanket.

The larynx and oesophagus were divided and retracted cranially to expose the left carotid sinus. The left lingual artery was cannulated leaving the tip of the cannula in the common carotid artery approximately 5 mm caudal to the carotid body. Heparinized saline (0.5 ml of 500 units ml^{-1}) was administered every 30 min to prevent clotting.

Neural activity

The carotid sinus nerve was sectioned proximally at its junction with the glossopharyngeal nerve and dissected free towards the carotid body.

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Exposed tissues were covered with liquid paraffin at 37 °C. The sinus nerve was desheathed and positioned on a supporting, earthed, stainless steel plate. Small bundles of fibres containing single active chemoreceptor units were suspended from one pole of a bipolar platinum electrode. An isolated piece of glossopharyngeal nerve of thickness similar to the active bundle was suspended between the plate and the other pole of the electrode. The sympathetic supply to the carotid body, which arises from the superior cervical ganglion, was identified.

A Digitimer Neurolog system was used for processing neural activity. The signal was amplified (NL 100 AK and 104) and filtered (NL 125). A window height discriminator (NL 200) was set to trigger a standard pulse, the frequency of which was displayed either as the output of an instantaneous ratemeter (NL 256) or integrated (NL 601) over pre-set periods of 1–20 s (NL 304). Integrated discharge was counted and printed automatically. The amplified and filtered signal was fed into an audio amplifier (NL 120) and speaker.

Chemoreceptors were identified by their random pattern of discharge which was increased in response to hypoxia, hypercapnia and bolus injection of NaCN 10 µg intracarotid. Integrated or instantaneous chemoreceptor discharge, arterial pressure and tracheal carbon dioxide and oxygen concentrations were recorded continuously on a chart recorder (Electromed). During administration of the volatile anaesthetics, tracheal anaesthetic concentration was recorded in place of oxygen. Action potentials were monitored on a digital storage oscilloscope (Tektronix).

Effects of volatile anaesthetics on oxygen and carbon dioxide response curves

Control curves of the responses of single chemoreceptor fibres to changes in Pa_{O_2} were obtained by varying Pa_{O_2} in the range 4–24 kPa (four points) at constant, normocapnic Pa_{CO_2}. Two minutes was allowed for stabilization after each change of the inspired gases before averaging steady-state afferent nervous discharge over four consecutive 20-s periods. At the end of the first of these counts, arterial blood was sampled for gas analysis. A plot was made of chemoreceptor activity (impulses s^{-1}) against Pa_{O_2} (kPa). An identical procedure was used to produce two-point responses to changes in Pa_{CO_2} in the range 3.3–13.3 kPa at constant, normoxic Pa_{O_2}.

The concentration of anaesthetic delivered to the airway by the Goldman vaporizer was adjusted manually to achieve and maintain the desired end-tidal concentration, monitored by the Normac analyser. The effect of the "on transient" of volatile anaesthetic administration on spontaneous chemoreceptor activity was examined by determining the percentage change in discharge frequency from baseline, at 1 and 9 min after onset, during constant ventilation with air. The steady-state responses to hypoxia (four points) and hypercapnia (two points) were measured subsequently. For the steady-state responses, adjustments to the ventilator were made as required to compensate for Pa_{CO_2} changes caused by the anaesthetic. Having recorded these data, administration of the volatile anaesthetic was stopped and 20 min recovery allowed before recording further control responses. Figure 1 illustrates an experimental record produced when determining the steady-state response to hypoxia and hypercapnia during administration of enflurane. In most experiments all three anaesthetics were tested on the same single fibre, in a random order. Control response curves to oxygen and carbon dioxide were obtained between each anaesthetic test.

For control and test oxygen responses, a best-fit curve (estimated by eye) was drawn with a flexiruler through the points obtained at the measured Pa_{O_2} values, as shown in figure 4. For control and test carbon dioxide responses, all data were plotted and linear regression used to fit the best carbon dioxide response under control and test conditions. The discharge at four selected values of Pa_{O_2} (5.3, 8, 13.3 and 18.7 kPa) and two selected values of Pa_{CO_2} (4 and 8 kPa) was determined by interpolation from the response curves. The interpolated values were used to produce average responses to the stimulus during control and test conditions at each level of stimulation. A paired *t* test was used to analyse the significance of the difference between control discharge and discharge during administration of volatile anaesthetic at each level of stimulation.

The volatile anaesthetics and the respective end-tidal concentrations tested were; 0.5–1.0% halothane (five cats and five rabbits); 0.6–1.0% enflurane (seven cats and four rabbits) and 0.5–1.0% isoflurane (eight cats and four rabbits). The majority of tests (72%) were performed using an end-tidal anaesthetic concentration of 0.8–1.0%; smaller concentrations were used only

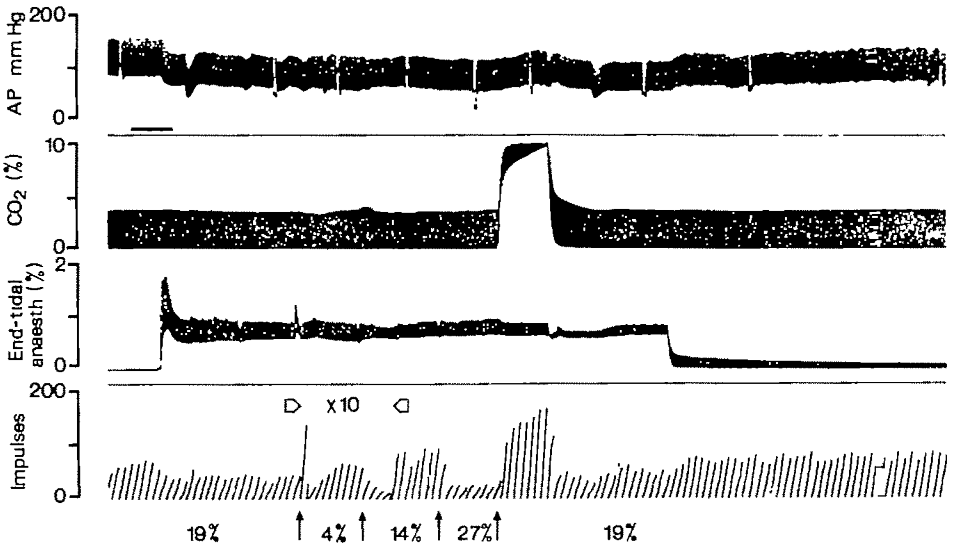

FIG. 1. Experimental record produced when determining the "on transient" and steady-state responses of a single chemoreceptor fibre to enflurane in the rabbit. From above downwards: arterial pressure (AP) (mm Hg); tracheal carbon dioxide (%) (end-tidal is the top edge of compressed trace, except at high carbon dioxide); tracheal anaesthetic concentration (%) (end-tidal is lower edge of compressed trace except in wash-out); integrated chemoreceptor discharge (impulses s^{-1}) resetting at 20-s intervals. Solid arrows beneath chemoreceptor discharge indicate points where tracheal oxygen (% indicated) was changed. Open arrows indicate change in gain (× 10) of scale for integrated discharge (max = 2000 impulses) during hypoxia. Interruptions in AP trace are caused by blood sampling for gas analysis. Horizontal time bar represents 2 min.

when mean arterial pressure decreased to less than 80 mm Hg in spite of a 15-ml infusion of gelatin solution. These instances were distributed evenly between the three volatile agents and the two species. Anaesthetic concentrations were not expressed in terms of MAC values because the concentration for 1 MAC may vary between species. The end-tidal $P\text{CO}_2$ was consistently lower than Pa_{CO_2}, the difference never exceeding 0.5 kPa. It is thus reasonable to assume that arterial partial pressures of volatile anaesthetics were also close to end-tidal ones.

The effects of cutting the sympathetic supply to the carotid body were examined in eight cats as follows: after the first three oxygen/carbon dioxide response curves (control, volatile agent, control) the sympathetic supply to the carotid body was divided whilst maintaining the recording from the same single fibre. A further three runs were conducted, testing the same anaesthetic after sympathectomy. The changes in discharge rate at $P\text{O}_2$ 13.3 kPa and constant $P\text{CO}_2$ caused by the anaesthetic were compared before and after sympathectomy.

RESULTS

Effects of the "on transient"

On introduction of each of the volatile anaesthetics into the inspired gases during normoxia/normocapnia, there was a marked decrease in spontaneous chemoreceptor discharge frequency over the first 1 min (fig. 2), followed by a variable degree of recovery towards control discharge (tables I, II).

TABLE I *Effects of the "on transient" of volatile anaesthetic administration on chemoreceptor discharge in the rabbit (mean (SEM))*

		Depression from control discharge at 1 and 9 min after administration of volatile anaesthetic (%)	
Anaesthetic	*n*	1 min	9 min
Halothane	5	19.4 (8.7)	3.0 (12.3)
Enflurane	4	42.0 (7.0)	36.0 (5.1)
Isoflurane	4	14.7 (15.1)	−9.6 (24.4)

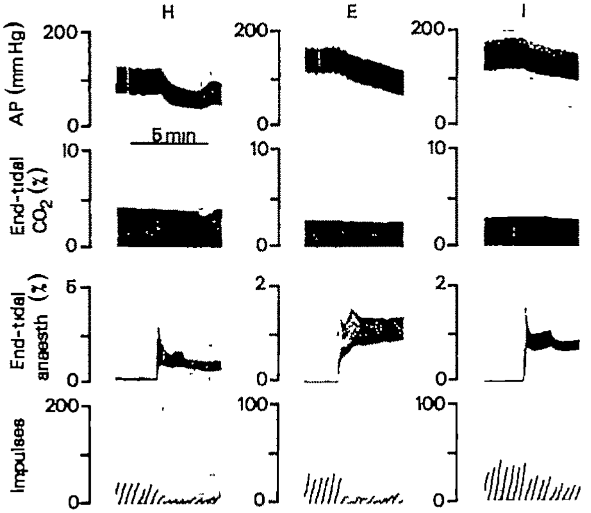

FIG. 2. "On transient" effects of halothane (H), enflurane (E) and isoflurane (I) on chemoreceptor discharge, arterial pressure (AP) (mm Hg) and end-tidal carbon dioxide (%) in the cat. Lower trace is integrated chemoreceptor discharge resetting at 20-s intervals. Note the different scale for end-tidal anaesthetic concentration in (H) and the decrease in AP and end-tidal carbon dioxide accompanying administration of all three anaesthetics. Slight recovery of AP in (H) was caused by gelatin 15 ml i.v.

The averaged response of the mean arterial pressure (MAP) to the onset of administration of the volatile anaesthetics is shown in table III for both rabbit and cat. There was a reduction of MAP in all instances on administration of the anaesthetics, but this effect was more marked in the cat. The reduction in MAP was often associated with a reduction in end-tidal carbon dioxide and Pa_{CO_2}, and an increase in Pa_{O_2}.

Effects on the hypoxic response in the steady-state

In both rabbits and cats the volatile anaesthetics predominantly depressed the chemoreceptor response to hypoxia (fig. 3). In only three fibres was the oxygen response curve shifted upwards—all by halothane. The overall effect of halothane in the cat was a small depression of the oxygen response, although only one of the four points was significantly different ($P < 0.05$; paired t test) from the control response. In the rabbit the inconsistency of the individual responses of fibres to halothane resulted in no change of the averaged halothane oxygen response curve from control. Enflurane depressed significantly the averaged oxygen response curve in both rabbit and cat ($P < 0.05$). Depression was more marked in the rabbit, but in both species this effect tended to be greater in hyperoxia than hypoxia. In the cat, isoflurane caused a marked depression of the averaged oxygen response curve which was statistically significant at all four levels of Pa_{O_2} measured. In the rabbit this response to isoflurane was less evident.

TABLE II. *Effects of the "on transient" of volatile anaesthetic administration on chemoreceptor discharge in the cat (mean (SEM))*

Anaesthetic	n	Depression from control discharge at 1 and 9 min after administration of volatile anaesthetic (%)	
		1 min	9 min
Halothane	4	71.9 (5.7)	47.1 (9.3)
Enflurane	4	71.7 (4.9)	36.7 (14.8)
Isoflurane	5	36.7 (10.8)	22.8 (15.7)

The depressant effects of the anaesthetics upon chemoreceptor activity were most apparent at high Pa_{O_2}. At Pa_{O_2} values less than 5.3 kPa, the depressant effects of the anaesthetics were always absent, as shown in the representative example of figure 4, even when there was a clear and reproducible effect at higher Pa_{O_2}.

Effects on the hypercapnic response in the steady-state

The predominant effect of all three anaesthetics on the carbon dioxide response curve was a downwards shift. This shift was parallel in 54% of fibres, accompanied by a decrease of slope in 23% and an increase of slope in another 23%. Paired t tests on the averaged grouped data from both rabbits and cats at two values of Pa_{CO_2} (4 and 8 kPa), showed that none of the anaesthetics caused a statistically significant change ($P > 0.05$) in the carbon dioxide response curves (fig. 5).

Effects of sympathectomy in the cat

After sympathectomy the rate of discharge increased slightly in all but three instances. The effect of the anaesthetics upon the chemoreceptor discharge persisted, and the degree of depression was identical to that seen before sympathectomy (table IV).

Pentobarbitone, infused directly into the carotid artery at a rate (0.35 mg min^{-1}) twice that used for i.v. maintenance of anaesthesia, caused a small increase in chemoreceptor discharge (8% of baseline value, in normoxia/normocapnia) in two rabbits.

TABLE III. *Effects of volatile anaesthetics, at steady state, on mean arterial pressure of rabbits and cats (mean (SEM)) during control (C) and during anaesthetic administration (A)*

	Mean arterial pressure (mm Hg)			
	Rabbit		Cat	
Anaesthetic	C	A	C	A
Halothane	102.0 (5.6)	75.0 (5.9)	90.0 (10.8)	53.8 (2.4)
Enflurane	101.3 (6.6)	73.8 (7.5)	114.0 (9.1)	67.0 (3.0)
Isoflurane	98.8 (8.3)	73.8 (4.7)	124.0 (6.8)	71.0 (3.7)

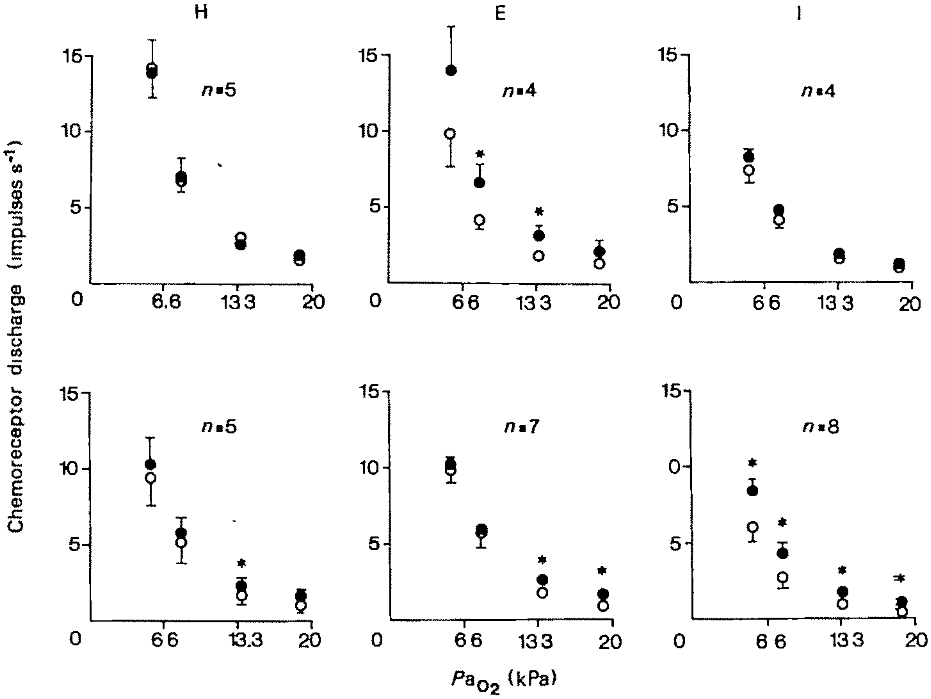

FIG. 3. Effects of 0.5–1.0% end-tidal halothane (H), enflurane (E) and isoflurane (I) on the oxygen response curves of chemoreceptor fibres in the rabbit (top) and cat (bottom). Data points represent mean chemoreceptor discharge (SEM bars) (impulses s^{-1}) at four values of Pa_{O_2} (kPa) for *n* fibres during control (closed symbols) and during administration of anaesthetic (open symbols). Where SEM bars are not shown they fall within the size of the symbol. *Significantly different ($P < 0.05$).

TABLE IV. *Steady-state discharge (impulses s^{-1}) of eight single fibres, from the sinus nerve of the cat, at constant Pa_{O_2} (13.3 kPa) and constant Pa_{CO_2} (3.7–4.2 kPa) and pH (7.28–7.42). Each set of four numbers represent values obtained from one fibre. Anaesthetic end-tidal concentrations were constant for each fibre in the range 0.6–1.0%. Base. = Baseline discharge; Iso. = isoflurane; Hal. = halothane; Enf. = enflurane*

	Base.	Iso.	Base.	Iso.	Base.	Hal.	Base.	Enf.
Before symp.	3.0	0.8	1.4	0.7	1.9	1.2	1.6	1.5
After symp.	2.5	0.5	1.0	0.5	4.2	3.5	1.6	1.6
Before symp.	0.6	0.5	1.0	0.6	1.5	1.4	2.5	2.2
After symp.	0.8	0.6	1.2	0.7	1.7	1.6	2.6	2.2

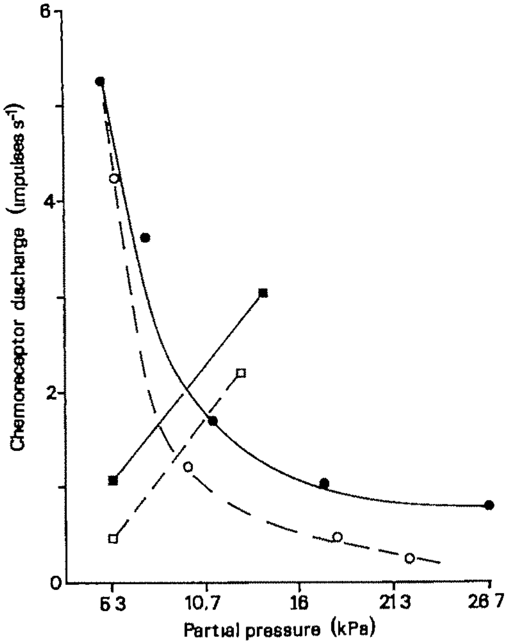

FIG. 4. Effect of 1.0% end-tidal halothane on the oxygen (○) and carbon dioxide (□) response curves of a chemoreceptor fibre in the cat. Abscissa represents partial pressure of oxygen or carbon dioxide in arterial blood (kPa). ● = Oxygen, control; ■ = carbon dioxide, control.

DISCUSSION

The results of this study demonstrate that doses of up to 1% enflurane and isoflurane have mildly depressant effects on steady-state chemoreceptor discharge in rabbit and cat, comparable to the effects described previously for similar doses of halothane in the cat [6, 7]. In contrast, the effects of halothane on the rabbit carotid body chemoreceptor discharge were almost absent. This species difference was apparent also with isoflurane, which proved to be a more potent chemodepressant in the cat. Enflurane emerged as the most consistent chemodepressant in the two species. This is significant clinically as, in man, enflurane has approximately half the anaesthetic potency of the other two agents tested. If the chemodepressant effect of enflurane in man is similar to that in the cat or rabbit, there will be a considerable effect at MAC values. This result is in agreement with the observations of Hirshman and colleagues [5] on the effects of volatile anaesthetics on the hypoxic ventilatory response in dogs.

Our observation that the chemodepressant effect of the anaesthetics was absent at Pa_{O_2} values less than 5.3 kPa is consistent with previous reports [7]. This suggests that, in severe hypoxia, chemoreceptor drive to the respiratory centres from the carotid bodies remains intact in spite of the anaesthetic, although the response at more moderate values of hypoxia may be attenuated. At least part of the depression of the ventilatory response to hypoxia by volatile anaesthetics recorded in the dog [5, 8] would, appear, therefore, to be caused by an effect on the carotid body chemoreceptors.

Although the carbon dioxide response curve was also shifted downwards, the slope was not affected greatly by the volatile anaesthetics, contrary to previous observations [7]. Depression of the hypercapnic ventilatory response recorded in the dog [5, 8] is likely, therefore, to be caused by a central effect of the volatile anaesthetics, rather than an effect on the carotid body chemoreceptors.

The more marked chemodepression at the on transient compared with the steady-state response to the anaesthetics was probably caused by a reduction in Pa_{CO_2} resulting from a reduction in cardiac output at constant ventilation. Although the gas changes were adjusted for the steady-state test, hypotension could not be compensated fully by infusion of gelatin. However, previous reports suggested that the observed reductions in MAP in our steady-state experiments were too small to cause detectable changes in chemoreceptor discharge in normoxia [9] or even in hypoxia [10], as MAP was maintained at or greater than 80 mm Hg. A drastic reduction in MAP results invariably in an increase in chemoreceptor discharge rate with a characteristic pattern of high variability in spite of constant blood-gas tensions. Such events were often recognized (and discarded) in our experiments when end-tidal concentrations of anaesthetics close to 1% were attempted. The mechanism of these changes is most likely reduced perfusion through the receptor tissue [9–11]. Thus the depressant effects of the anaesthetics could not have been mediated by the accompanying reduction in MAP, as the effect of the latter is an increase in discharge.

The on transients of halothane and enflurane caused greater chemodepression than isoflurane (tables I, II) which supports further a mechanism of chemodepression involving a reduction in cardiac output because, in the rabbit dog and man, halothane [12, 13] and enflurane [14] cause hypotension primarily by a reduction in cardiac output. On the other hand, isoflurane acts pri-

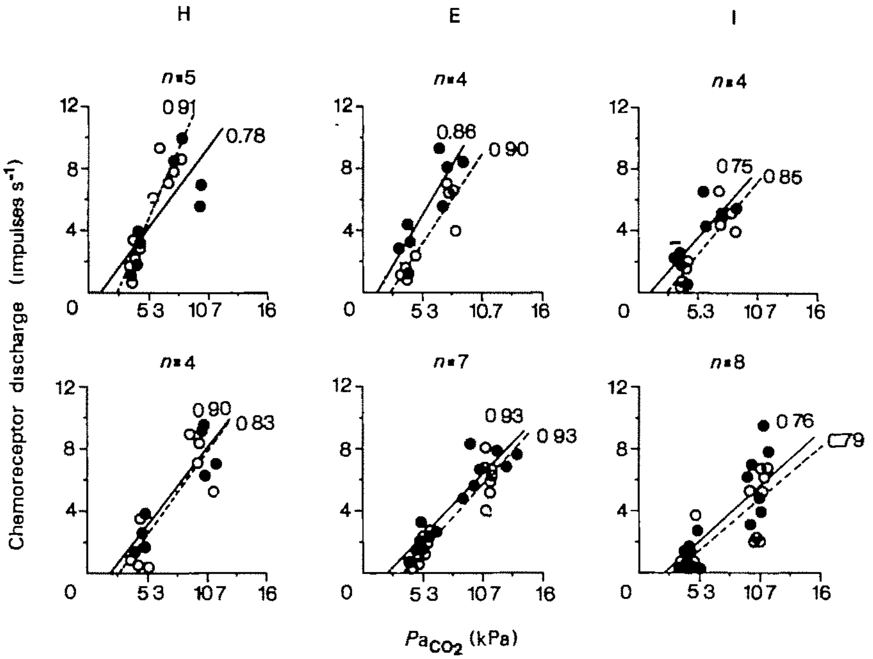

FIG. 5. Effects of 0.5–1.0% end-tidal halothane (H), enflurane (E) and isoflurane (I) on the slope of the carbon dioxide response curves of chemoreceptor fibres in the rabbit (top) and cat (bottom). Data points represent individual measurements of chemoreceptor discharge at normocapnia and hypercapnia for *n* fibres during control (●) and during administration of anaesthetic (○). Regression lines have been drawn through the data points (—— = control; – – – = anaesthetic) and the regression coefficients calculated.

marily on peripheral vascular resistance. The tendency for chemoreceptor activity to recover partially, spontaneously, over the first 9 min of anaesthetic administration may be a result of reflex increase in cardiac output.

It is unlikely that background anaesthesia with pentobarbitone affected chemoreceptor discharge directly [6], or indirectly by altering the character of the responses to the volatile anaesthetics. In support of this, the reported effects of halothane on cat chemoreceptor discharge [6, 7] are almost identical, even though one group [7] used decerebrate animals (without background pentobarbitone anaesthesia). In addition, our own results with thiopentone [15] indicate that larger doses of barbiturates injected into the carotid artery have only a moderate effect upon chemoreceptor discharge.

There are several possible explanations for the depressant effects of volatile anaesthetics on chemoreceptor activity. If the volatile anaesthetics cause chemodepression secondary to vasodilatation of the carotid body vasculature and increased blood flow, as proposed by Biscoe and Millar [6], one might expect to see a potency in the order: isoflurane > halothane > enflurane, as this is their order of potency as vasodilators in man and dog [16–18]. The combined results for both rabbits and cats, however, indicate that enflurane was the most consistent in its chemodepressant effect.

Chemodepression is unlikely to occur via a reduction in sympathetic tone, as sympathectomy did not alter chemodepression secondary to the volatile anaesthetics, confirming the results of Biscoe and Millar [6] for halothane in the cat.

There is the possibility that the anaesthetics increase the release of endogenous dopamine in the carotid body, which has a chemodepressant effect in both cats and rabbits [19], but this hypothesis was not tested. Modulation of neurotransmitter release by anaesthetics in the CNS has been demonstrated [20].

It is most likely that the volatile anaesthetics exert a direct action upon the chemoreceptor mechanism. This is difficult to prove, as neither the chemoreceptor transduction process nor the mechanism of action of anaesthetics are fully understood.

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EFFECT OF THIOPENTONE, ETOMIDATE AND PROPOFOL ON CAROTID BODY CHEMORECEPTOR ACTIVITY IN THE RABBIT AND THE CAT

J. PONTE AND C. L. SADLER

SUMMARY

The response of the carotid body chemoreceptors to intracarotid administration of thiopentone, etomidate and propofol was tested in the rabbit and cat. Thiopentone 3–6 mg min^{-1} and etomidate 300–600 μg min^{-1} were mildly excitatory, shifting the oxygen and carbon dioxide response curves upwards. Propofol 1.5–3.0 mg min^{-1} was a potent chemodepressant and abolished discharge at Pa_{O_2} values greater than 8 kPa. Prolonged infusion of propofol at higher rates (6 mg min^{-1}) abolished the response to hypoxia completely. The significance of these results is discussed in relation to the known ventilatory effects of the three anaesthetics.

A period of apnoea is often associated with induction of anaesthesia with thiopentone [1, 2], etomidate [3] and propofol [1, 2, 4, 5]. Thiopentone also reduces the respiratory response to hypercapnia [6]. The role of the carotid body chemoreceptors in the ventilatory responses to these i.v. anaesthetics is unknown. We have investigated, therefore, the effects of thiopentone, etomidate and propofol on the activity of single afferent chemoreceptor fibres in the rabbit and cat. Some of the results for propofol have been published in brief [7].

METHODS

Experiments were performed on five New Zealand White rabbits and three cats. Anaesthesia, dissection and recordings of neural activity were identical to the methods described in the accompanying paper [8].

Effect of anaesthetics on oxygen and carbon dioxide response curves

Control reponses of single chemoreceptor fibres to oxygen and carbon dioxide were constructed over the ranges 4–24 kPa and 3.3–13.3 kPa, respectively, using the methods described by Ponte and Sadler [8]. This procedure was repeated while anaesthetic drugs were infused at a constant rate into the common carotid artery (i.c.) during steady-state conditions. The infusion was stopped and control responses re-established under steady-state conditions after 20 min recovery.

The anaesthetics studied were: thiopentone 0.6–16.0 mg min^{-1} (two cats and one rabbit); etomidate 300–600 μg min^{-1} (three cats and three rabbits); propofol 0.3–3.0 mg min^{-1} (three cats and three rabbits). The infusion rates tested ranged from the lowest value that produced a detectable effect upon chemoreceptor discharge, up to values causing severe hypotension.

Thiopentone was dissolved in isotonic saline to a concentration of 10 mg ml^{-1}. Etomidate was first dissolved in Cremophor EL 10 mg ml^{-1} before dissolving this mixture in saline 10 ml to give etomidate 1 mg ml^{-1} in a 10% solution of Cremophor–saline. Propofol was supplied and administered in 10% Intralipid at a concentration of 10 mg ml^{-1}. The drugs were infused at room temperature and equilibrated with air. The response of the chemoreceptors to the solvents when infused at the maximum volumetric rate used for drugs (1.6 ml min^{-1}) was tested. The effect of the anaesthetics on local blood pH in the carotid body was estimated by recording the change in pH on mixing thiopentone 10 mg ml^{-1}, etomidate 1 mg ml^{-1} or propofol 10 mg ml^{-1} with

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blood to a 1 in 10 dilution *in vitro*, in a closed cuvette.

Blood flow through the common carotid artery of the anaesthetized cat and rabbit has not been measured. From other data regarding renal artery, hepatic artery and total cerebral blood flow [9], however, we estimated that blood flow in each common carotid artery in both species lies between 2 and 10 % of the cardiac output; that is 4–20 ml min^{-1}/kg body weight. If this estimate is correct, the local blood concentrations produced by our infusions would be in the ranges of 10–13 μg ml^{-1}, 5–50 μg ml^{-1} and 5–250 μg ml^{-1} for thiopentone, etomidate and propofol, respectively.

During the chemodepression caused by propofol, bolus injections of potassium chloride 10 μmol litre $^{-1}$ in 0.5 ml saline intracarotid (i.c.) were given in order to determine the excitability of sinus nerve endings. The effect of an i.v. injection of propofol 2 mg kg^{-1} on chemoreceptor discharge was also examined.

RESULTS

On mixing thiopentone 10 mg ml^{-1}, etomidate 1 mg ml^{-1} and propofol 10 mg ml^{-1}, with blood *in vitro* to form a 1 in 10 dilution, blood pH increased by 0.1, 0.04 and 0.03 units, respectively.

Thiopentone 3–6 mg min^{-1} i.c. increased chemoreceptor discharge in the two cats and one rabbit tested, shifting the oxygen response curve upwards, as illustrated in figure 1A for the rabbit. Table I shows the average effect at normoxia/normocapnia. Higher doses (16 mg min^{-1} i.c.) progressively depressed activity until there was no discharge; at this point activity could not be elicited by hypoxia (Pa_{O_2} 4 kPa).

Etomidate 300–600 μg min^{-1} also increased chemoreceptor discharge causing an upward shift of the oxygen and carbon dioxide response curves in all three cats and one of three rabbits tested, as illustrated in figure 1B for the rabbit. The average values of afferent discharge and arterial pressure, in normoxia/normocapnia, during six i.c. in-

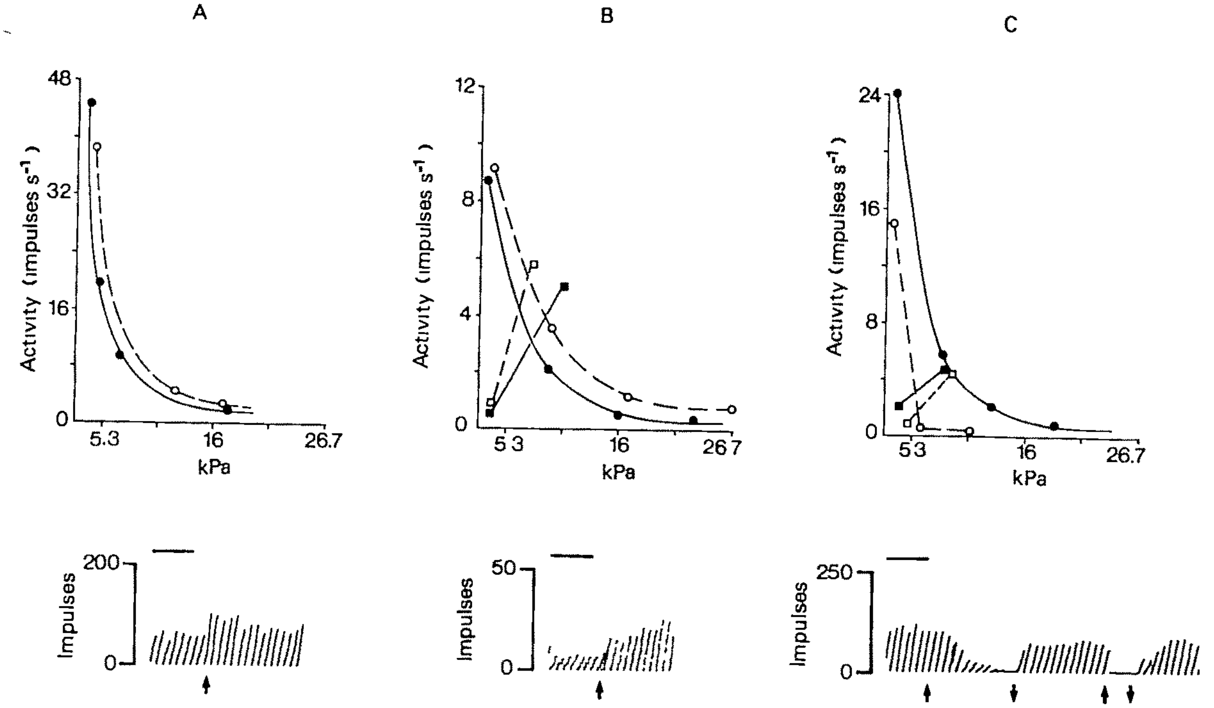

FIG. 1. Effects of i.c. infusions of A: thiopentone 6 mg min^{-1}; B: etomidate 600 μg min^{-1}; C: propofol 1.5 mg min^{-1} on chemoreceptor activity in the rabbit. Top shows effects on oxygen (○) and carbon dioxide (□) response curves. ● = Oxygen control; ■ = carbon dioxide control. Ordinates represent chemoreceptor activity (impulses s^{-1}) and abscissa represents partial pressure of oxygen or carbon dioxide in arterial blood (kPa). Bottom shows initial response of integrated chemoreceptor discharge (resetting every 20 s) to the "on transient" (at arrow) of the anaesthetic infusion given above. Time bar = 2 min.

TABLE I. *Effects of intracarotid infusions of anaesthetics upon chemoreceptor afferent discharge (I/S) at normoxia/normocapnia. Where* n = 6, *results are from three cats and three rabbits. Where* n = 3, *results are from two cats and one rabbit. Means (SEM).*

	I/S	Pa_{O_2} (kPa)	Pa_{CO_2} (kPa)	MAP (mm Hg)	*n*
Control	1.6 (1.3)	14.49 (1.59)	3.96 (0.35)	93.3 (17.5)	6
Etomidate 600 μg min^{-1}	2.6 (2.2)	14.81 (1.52)	4.07 (0.13)	86.8 (14.1)	6
Control	2.5 (2.3)	15.07 (2.59)	4.09 (0.20)	91.3 (16.3)	6
Propofol 1.5 mg min^{-1}	0.9 (1.0)	14.73 (2.09)	4.11 (0.31)	85.5 (14.2)	6
Control	1.7 (0.8)	13.77 (2.29)	4.19 (0.37)	79.0 (18.5)	3
Thiopentone 3 mg min^{-1}	2.7 (1.4)	14.57 (1.76)	4.24 (0.15)	75.0 (21.8)	3

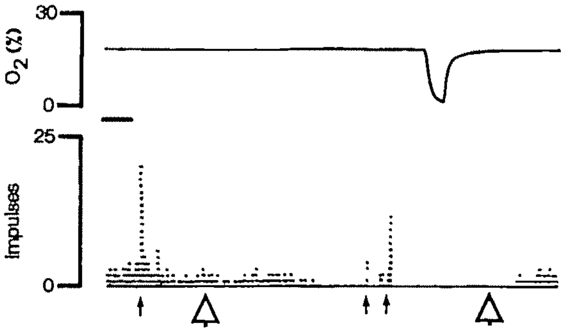

FIG. 2. Inhibitory effect of propofol 6 mg min^{-1} i.c. (between open arrows) on chemoreceptor discharge (integrated over 1-s periods) in the cat. Silencing of the fibre could be reversed by potassium chloride 10 μmol i.c. (at solid arrows), but not by hypoxia (3.6 kPa). Upper trace represents tracheal oxygen. Time bar = 1 min.

fusions of 600 μg min^{-1} are shown in table I. The stimulatory effect was reduced in hypoxia. Etomidate had very little effect, up to the highest rate used, in two of the rabbits.

Propofol 1.5–3.0 mg min^{-1} was a potent chemodepressant in all animals tested, as illustrated in figure 1c for the rabbit, shifting the oxygen and carbon dioxide response curves downwards. Average values of afferent discharge and mean arterial pressure, in normoxia/normocapnia, during six i.c. infusions of propofol 1.5 mg min^{-1} are shown in table I. Three of these fibres were silenced reversibly by propofol at rates of infusion of 3 mg min^{-1} at Pa_{O_2} values greater than 8 kPa; activity reappeared at Pa_{O_2} 5.3 kPa and less. Higher rates of propofol infusion (6 mg min^{-1}) abolished also the response to hypoxia but not to potassium chloride (fig. 2). Even at these higher rates of i.c. infusion, chemodepression caused by propofol was rapidly reversible on stopping administration. I.v. injection of propofol 2 mg kg^{-1} also caused chemodepression, although this was less marked (fig. 3).

All three anaesthetics caused a small progressive reduction in mean arterial pressure during intracarotid infusion (table I); when the highest rates of infusion were used hypotension was more marked and data were discarded if the pressure decreased to less than 60 mm Hg.

Cremophor in the doses used for administration of etomidate had no effect on chemoreceptor

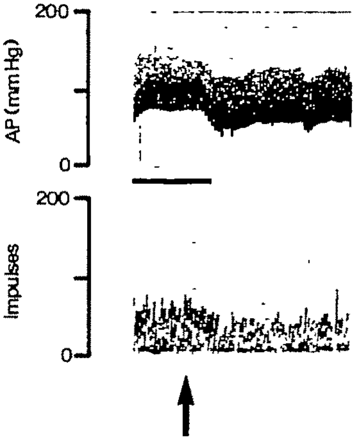

FIG. 3. Effect of an i.v. injection of propofol 6 mg (at arrow) on systemic arterial pressure (mm Hg) and chemoreceptor discharge (impulses integrated over 2-s periods) in the rabbit. Time bar = 1 min.

discharge. At much higher doses (20% Cremophor 1.5 ml min^{-1} i.c.) there was only a mild stimulation of discharge. Intralipid, infused at rates three times greater (1.5 ml min^{-1} i.c.) than maximum used for propofol adminstration, and saline at the highest rate used for thiopentone (1.6 ml min^{-1} i.c.) did not affect discharge (fig. 4).

DISCUSSION

Biscoe and Millar [10] reported that bolus i.v. administration of pentobarbitone 6–12 mg had little effect on chemoreceptor discharge in the cat. It is unlikely, therefore, that the maintenance dose of pentobarbitone used in our study (4–6 mg kg h^{-1}) had any effect on the response of the chemoreceptors to the three anaesthetics tested.

Assuming a blood flow through the carotid body of 20 ml min^{-1} in a 3-kg animal (see methods) and taking an average rate of drug infusion equal to 0.5 ml min^{-1}, there is a 1 in 40 dilution of the solution given via the intracarotid route. The small changes in blood pH measured *in vitro* for a 1 in 10 dilution of thiopentone should therefore represent an overestimate (at least 4 times) of the local blood pH changes *in vivo*. However, the changes in activity caused by thiopentone were in the opposite direction of that expected from the pH changes. It is thus unlikely that the observed effects of thiopentone were secondary to a change in blood pH. For the same reason, the accompanying possible Pa_{CO_2} change when the pH is increased by addition of a fixed base cannot explain the increase in activity either. It is more likely that thiopentone acted in a way analogous to metabolic poisons such as amytal which blocks the mitochondrial electron transport chain. The pH changes caused by the addition of

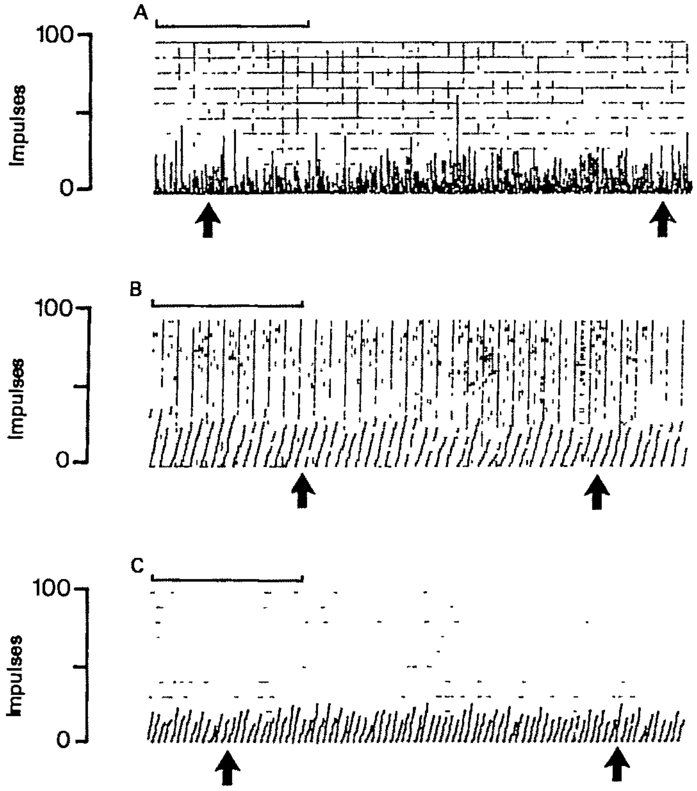

FIG. 4. Effects of intracarotid infusions (between arrows) of three solvents upon chemoreceptor activity at normoxia/normocapnia, mean arterial pressure 85–110 mm Hg. A: Cremophor 20% in saline at 1.5 ml min^{-1}, in the cat: instantaneous activity of two afferent chemoreceptor fibres in impulses per second (time bar = 2 min); note slight increase in activity throughout infusion. B: Intralipid 10% at 1.5 ml min^{-1}, in the cat; integrated activity of a single fibre over 20-s periods (time bar = 5 min). C: Normal saline 1.6 ml min^{-1}, in the rabbit; integrated activity of two fibres over 5-s periods (time bar = 2 min).

the solutions containing etomidate and propofol were far too small to explain the effects.

Our observations that thiopentone and etomidate were mildly chemoexcitatory may thus explain partially the brief period of hyperventilation which has been reported following administration of thiopentone [11] and etomidate [3] in man.

Our results also suggest that the period of apnoea following clinical administration of propofol [1, 2, 4, 5] may result at least partly from depression of afferent activity arising from the carotid body. Indeed, an i.v. dose of propofol smaller than the standard induction dose did cause a visible depression of activity in normoxia. The mechanism of this chemodepression is not clear, but it is unlikely to result from a local anaesthetic effect on the carotid sinus nerve terminals as bolus injections of potassium chloride 10 µmol i.c. could elicit discharge during profound propofol-induced chemodepression.

The effects of propofol on the carotid body are interesting and unique, as it could abolish chemoreceptor discharge reversibly, even in hypoxia, whilst maintaining the response to potassium chloride. This reproducible and very short lived effect makes propofol a useful tool for future investigations on the chemoreceptor transduction mechanism.

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COMPUTER CONTROLLED INFUSION OF PROPOFOL

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J. DIXON AND J. T. HARVEY

SUMMARY

A computer controlled infusion pump was used to deliver propofol to two groups of eight patients undergoing body surface surgery. The patients were premedicated with morphine sulphate i.m. and anaesthesia was supplemented with 66% nitrous oxide in oxygen. Patients in group 1 breathed spontaneously, whereas patients in group 2 underwent artificial ventilation to a normal Pa_{CO_2}. *The computer program was designed to achieve and maintain a blood concentration of propofol 3 µg ml*$^{-1}$ *as rapidly as possible, basing calculations on a three-compartment pharmacokinetic model. Mean blood propofol concentrations were found to be close to the predicted target from 10 to 120 min in group 1, but were 5–20% higher from 20 min in group 2.*

When anaesthesia is to be maintained by a constant rate i.v. infusion of propofol, induction is achieved usually by an initial single dose. This may result in an excessive peak in blood concentration and consequent sudden hypotension [1], with or without apnoea. If a smaller dose is used, a decrease in plasma concentration between 5 and 20 min may result with the consequent risk of inadequate anaesthesia at the beginning of surgery. To minimize undesired cardiovascular or respiratory changes during induction, and to ensure a predictable quality of anaesthesia, propofol should be administered using a system of infusion which rapidly and accurately attains and maintains a constant blood concentration of the drug.

The concept of an idealized i.v. drug input was introduced in 1966 by Kruger-Thiemer [2] and later applied to lignocaine therapy by Vaughan and Tucker [3]. Since then, computerized systems have been used successfully to achieve and maintain constant plasma concentrations of the i.v. anaesthetic etomidate, such as the bolus elimination transfer (BET) scheme described by Schuttler, Schwilden and Stoeckel [4], which based calculations on a two-compartment pharmacokinetic model. Following an initial loading dose which was calculated to increase the blood concentration to the required final concentration, an exponentially declining infusion was given.

This paper describes the development of a computerized system of propofol infusion which was designed to achieve constant blood concentrations rapidly in order to minimize the unwanted haemodynamic and respiratory effects, but provide satisfactory anaesthesia.

Theoretical basis

The disposition of infused propofol is assumed to be described by an equation representing a linear three-compartment model, with drug entering or leaving the system only by the first compartment (fig. 1):

$$\text{Blood concentration} = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t} + D$$

where the blood concentration = concentration in the first compartment; A, B, C and D are constants and α, β and γ are the exponential rate constants. A, B, C and D are constant only when describing a constant rate infusion of drug and become complex functions of time when describing an exponentially decreasing infusion.

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Initially, all compartments (fig. 1) have a drug (propofol) concentration of zero. To achieve the target blood concentration rapidly (volume 1 concentration), sufficient drug must be given as a single dose. If the blood concentration (i.e. that in volume 1) is to be kept constant, the amount of drug entering it and leaving it must be equal. Drug leaves the blood to pass into volumes 3 and 2 at a gradually decreasing rate as the concentrations in these compartments increase. Drug also leaves the blood because it is metabolized (mainly in the liver) at a clearance given by (k_{10} × volume 1) ml min^{-1}. As the blood concentration of drug is to be kept constant (C_{TG} = target concentration in µg ml^{-1}), the amount of drug cleared is given by:

$$(k_{10}) \times (\text{volume } 1) \times C_{TG}\ (\mu\text{g min}^{-1})$$

Theoretically, it would take an infinite time for the peripheral compartments to achieve the target concentration. For the slowest compartment to achieve at least 94 % of any target concentration, it would take approximately 16 h. Finally, when there was no further redistribution to other compartments, the amount of drug to be infused would be equal to that being cleared.

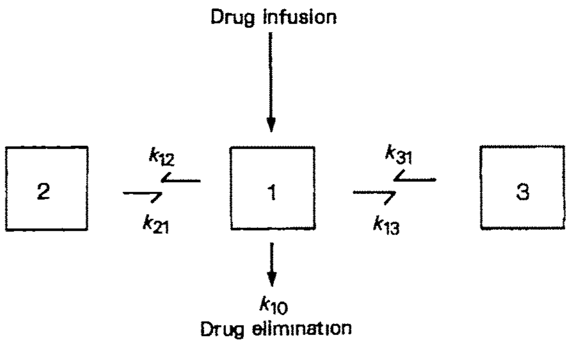

FIG. 1. The three-compartment pharmacokinetic model where 1, 2 and 3 represent the mathematical volumes of distribution. Volume 1 is the initial volume of distribution The intercompartmental and elimination rate constants are shown as *k* values.

METHODS

Infusion rate calculation

After the body weight and target concentration had been entered into the computer, the program calculated the infusion rate in three parts:

(1) An initial loading dose given over 20–30 s was given by:

LOADING DOSE = (target concentration × initial volume of distribution)

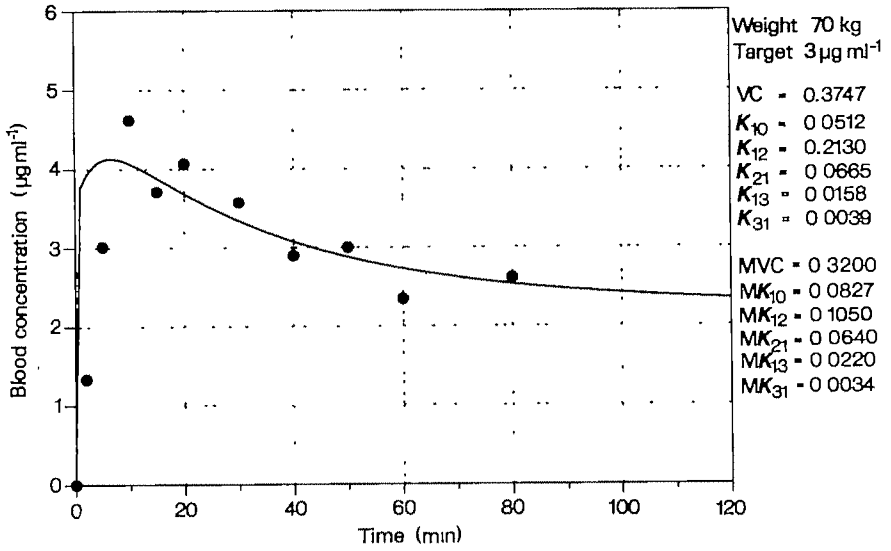

FIG. 2. Propofol concentrations generated when pharmacokinetic parameters from a single dose study were used in the infusion rate calculations. The black circles represent propofol concentrations which were measured during computerized infusion, using the same method as described in this paper. The continuous line shows the predicted propofol concentrations (using our computer model) following infusion rates calculated using *K* values derived from the single dose study and the *K* values of group 2 in the simulated patient.

(2) A constant infusion rate to equal the elimination of propofol from the blood was given by:

$$\text{LOADING DOSE} \times K_{10}$$

(3) A continuously decreasing infusion rate to match the distribution into the 2nd and 3rd compartments (for a full account of the mathematical derivation see reference [5]) was calculated as:

$$\text{LOADING DOSE} \times (K_{12}e^{-K_{21}t} + K_{13}e^{-K_{31}t})$$

These were calculated every 10 s by the computer program for the elapsed time (t). The values K_{12}, etc., are the assumed rate constants.

Computer model

In order to predict and examine the effects of using different pharmacodynamic data, we developed a computer model which allowed us to choose a set of rate constants and an initial volume of distribution for the infusion rate calculation in a simulated patient. In a pilot study we used pharmacokinetic parameters derived from a single dose study [6] because these were the only data available at the time, but this resulted in an early overshoot of propofol blood concentration (dark circles in figure 2). This method overestimated the initial volume of distribution because of the difficulty in estimating the initial rate of decay. We therefore progressed to pharmacokinetic parameters derived from infusion studies [7, 8] in which the alpha phase was estimated by fitting the curve both at the start and at the end of the infusion, and these were the values used for calculation of the infusion rates in group 1 (table I).

We later ran the model using the rate constants for group 2 as the "patient" values, and the rate constants from the single dose pharmacokinetic study [6] for the infusion rate calculations. We were interested to see that the predicted plasma concentration (solid line in figure 2) was very close to the concentrations actually measured in our preliminary runs.

TABLE I. *Values for the intercompartmental transfer constants used in groups 1 and 2 together with the initial volumes of distribution (Volume 1)*

	Group 1	Group 2
Volume 1 (litre kg^{-1})	0.25	0.32
K_{10} (min^{-1})	0.1058	0.0827
K_{12} (min^{-1})	0.144	0.105
K_{13} (min^{-1})	0.0282	0.022
K_{21} (min^{-1})	0.064	0.064
K_{31} (min^{-1})	0.0034	0.0034

The values for the parameters used in group 1 of this study (table I) were subsequently adjusted slightly, using the computer model, to improve the rate at which the target concentration was reached. In order to determine the pharmacokinetic profile which would achieve the target concentration most rapidly, different "patient" profiles were entered into the computer model. The same infusion profile was used as in group 1 patients. Each time the "patient" profile was changed, the resulting blood concentration curve was compared visually to that actually recorded in the group 1 patients. When adjusting the parameters, the clearance (k_{10} × volume 1) was kept constant. The adjusted values (table I, group 2) were thus assumed to represent more accurately the average pharmacokinetic profile of patients in group 1.

Equipment

An IMED 929 infusion pump was used to deliver the continuous infusion at rates ranging from 20 to 1200 ml h^{-1}. It was controlled through an RS232 interface from a BBC model B microcomputer (fig. 3) and the infusion rate and the total volume given by the pump were checked and adjusted every 10 s by the program. To improve the reliability of the system, extensive error trapping was built into the software and a mains filter fitted into the computer supply line.

Procedures

Group 1. Eight healthy patients aged 24–65 yr gave informed consent before taking part in the study. They were premedicated with morphine sulphate 0.15 mg kg^{-1} i.m. 1 h before induction. Herniorrhaphy was performed for two patients and the remainder underwent varicose vein surgery.

Two 16-gauge i.v. cannulae were inserted under local anaesthesia, one into a large forearm vein for infusion of propofol and the second into the largest contralateral antecubital fossa vein for sampling. All patients were monitored throughout with an electrocardiogram in the CM5 configuration and the arterial pressures were measured with a Dinamap 845 on the sampling arm.

Fifteen seconds after starting the computerized infusion, the patients were asked to breathe 66 % nitrous oxide in oxygen, from a facemask connected to a Mapleson A breathing system. Except

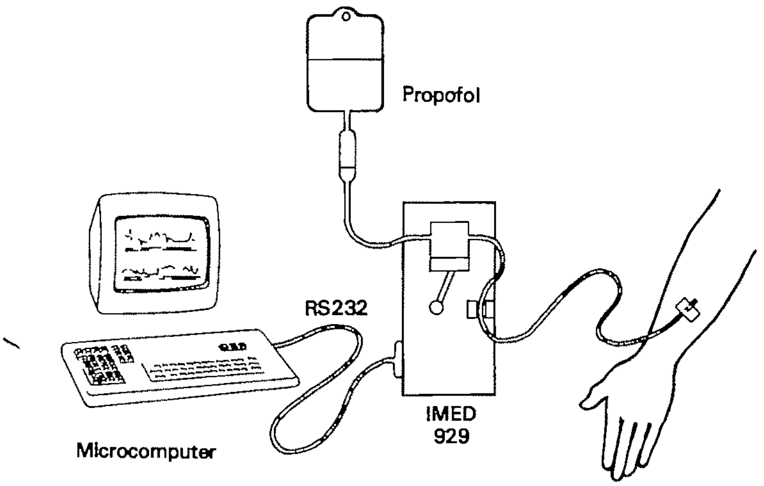

FIG. 3. A diagrammatic representation of the apparatus showing the connections between the BBC microcomputer, the IMED 929 infusion pump and the patient.

during intubation, spontaneous breathing was continued with this mixture until cessation of infusion. At 6 min, suxamethonium 1 mg kg^{-1} was given i.v. to facilitate intubation with a tracheal tube lubricated with lignocaine ointment and the lungs were ventilated by hand for a short period.

At the end of the operation the inspired gas mixture was changed to 100% oxygen, the infusion was stopped and the tracheal tube removed. The times to respond to command, to eye opening and giving correct date of birth were recorded.

Group 2. A further eight patients undergoing body surface surgery (aged 28–58 yr, ASA I or II) were studied. Premedication, induction, sampling and monitoring were the same as in group 1. Maintenance of anaesthesia was identical also, except that ventilation to normocapnia was achieved using a Penlon-Oxford ventilator in a partial rebreathing mode. No further neuromuscular blocking drugs were given.

Sampling and assay

Five-millilitre samples of venous blood were placed into tubes containing oxalate before induction of anaesthesia and at 2, 5, 10, 15, 20, 30, 40, 50, 60, 80, 100 and 120 min after starting the infusion. The samples were mixed well and kept at 4 °C until required for analysis. Whole blood propofol concentration was measured using HPLC with fluorescence detection [9].

To check the accuracy of the method, 11 blood samples from healthy volunteers were each mixed with propofol 1 μg ml^{-1} and measured. The results gave a mean value of 1.107 μg ml^{-1}, with a coefficient of variation of 6%. The limit of detection using this assay was 20 ng ml^{-1}.

RESULTS

In all patients the induction of anaesthesia was satisfactory, taking between 1 and 2 min from the start of infusion. There were no periods of apnoea longer than 15 s. At 6 min, conditions for intubation were good in all patients and there were no cases of awareness.

Group 1

Figure 4 shows the blood propofol concentrations in each of the eight patients. The mean blood propofol concentration was within 6% of the target concentration (3 μg ml^{-1}) by 10 min, and remained close for up to 120 min (fig. 5). The variation between patients was largest (coefficient of variation 43.8%) during the initial 2 min when the infusion rate was highest.

Although no patient moved in response to the initial surgical incision, a volatile agent was required for a short period in two patients. A lean man of 80 kg, who needed isoflurane during induction, was shown to have lower blood propofol concentrations than predicted.

By 60 min the infusion rate had decreased to 125% of the calculated final infusion rate which

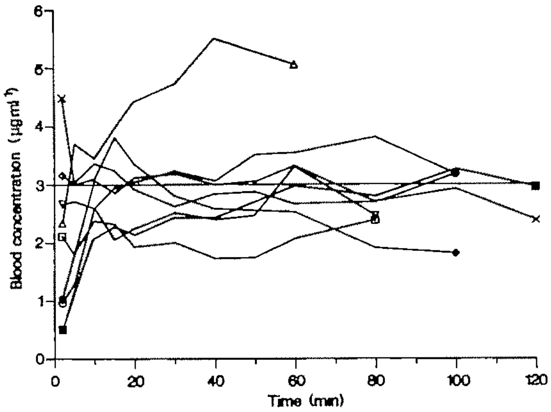

FIG. 4. Individual blood propofol concentrations for the eight patients in group 1. The target concentration is plotted as the bold line.

would be reached at equilibrium when all the compartments contain the same concentration (the steady state concentration: C^{ss}). It had decreased to 118 % by 120 min (table II).

Table II summarizes the total doses given and the time taken before the patients could give correct date of birth. The latter varied from 8 to 17.5 min following cessation of nitrous oxide and propofol, and was not related to weight ($r = 0.05$), total dose ($r = 0.24$) or duration of infusion. However, the blood concentration before switching off the infusion reached a nearly significant correlation ($r = 0.64$, $P < 0.06$).

Arterial pressure and heart rate decreased gradually, reaching steady values at about 15 min (fig. 6). Using a paired *t* test to analyse the decrease in systolic arterial pressure from its initial value over the first 20 min, there was a

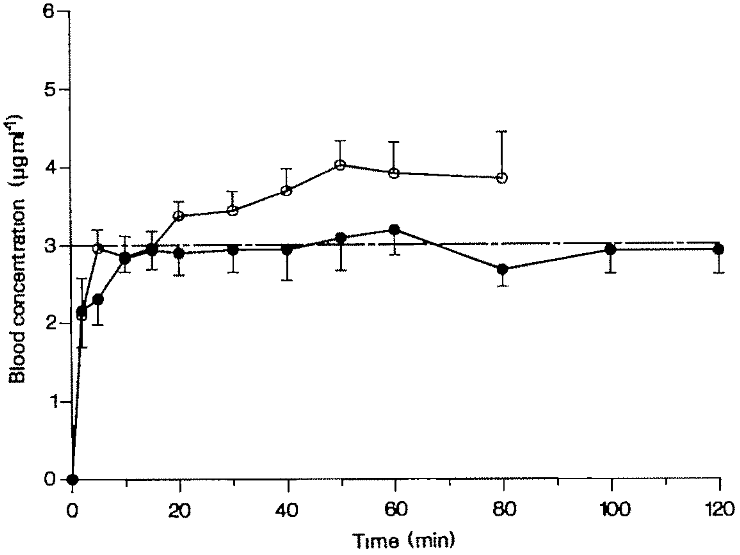

FIG. 5. Mean whole blood propofol concentrations of the 16 patients. Group 1 are represented with closed circles, group 2 open circles The error bars represent 1 SEM.

TABLE II. *A summary of the results of groups 1 and 2. Final I-rate = infusion rate at the end of anaesthesia. CSS I-rate = calculated rate which would be reached at steady state*

	Weight (kg)	Duration of infusion (min)	Total dose (mg kg⁻¹)	Final I. rate (ml h⁻¹)	CSS I. rate (ml h⁻¹)	Time to giving correct date of birth (min)
Group 1						
Mean	73	102	11	41	35	12
SD (range)	10.1	(64–129)	2	6.3	5	3.3
Group 2						
Mean	76	77	10	44	36	13
SD (range)	13.6	(45–135)	2.6	7.5	6.5	3.7

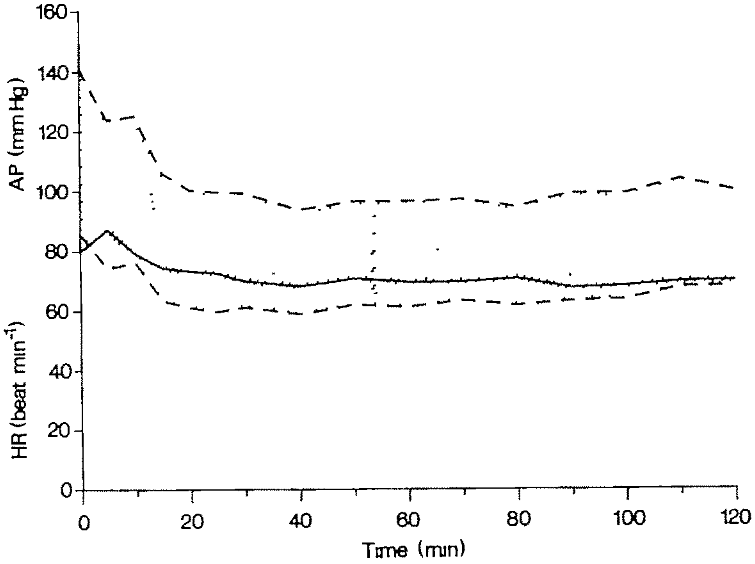

FIG. 6 Mean cardiovascular changes from the eight patients in group 1. The area between mean systolic and mean diastolic arterial pressures is shaded. Heart rate is shown as the continuous thick line.

significant change at 15 and 20 min ($P < 0.001$; level of significance taken as $P < 0.005$ because of a Bonferroni correction for multiple comparisons). The final mean values for systolic arterial pressure and heart rate were approximately 33% and 12% less than the starting values, respectively. The increase in systolic arterial pressure following intubation at 7 min was small, the mean value at 10 min being only 1% greater than that at 5 min.

Group 2

There was no significant difference in either age or weight between the two groups. The mean duration of infusion (77 min) was shorter in group 2 because the surgery finished earlier, with only one patient having an infusion longer than 80 min. Mean blood propofol concentrations for this group are shown in figure 5, and there was no significant difference (using multiple t tests with or without a Bonferroni correction) between the mean concentrations of the two groups at any time up to 80 min. The blood concentration was within 4% of the target by 5 min, which is sooner than in group 1 but not significantly so, and the mean concentrations began to exceed the target as the duration of infusion increased. Changes in haemodynamic variables were very similar to those in group 1.

DISCUSSION

Our main objectives in developing the system described in this paper, were to achieve stable and predictable blood concentrations of i.v. anaesthetics rapidly in order to improve clinical conditions particularly during the first 30 min of anaesthesia, and to study the pharmacokinetics of these drugs and their potential pharmacokinetic interactions with opioids and neuromuscular blocking drugs.

Many methods of rapidly achieving a steady state concentration of drugs have been described [10]. Most of these methods are approximate, and involve many different combinations of single doses or infusions, but one accurate method is the BET scheme described by Schuttler, Schwilden and Stoeckel [4]. This type of infusion has been used successfully with etomidate [4], fentanyl [5] and alfentanil [11]. McMurray and colleagues [12] described an application of the method of Riddell and co-workers [13] for generating a constant plasma concentration of methohexitone. The main infusion given was a low concentration of the drug, but it ran through a chamber of high concentration (which was gradually diluted) before reaching the patient and thus resulted in a decreasing infused drug concentration with a constant infusion rate.

We chose a target concentration of 3 μg ml⁻¹

because it is close to the EC_{95} for propofol [14] in morphine premedicated patients. We used a three-compartment pharmacokinetic model for propofol for two reasons: many of the studies performed to determine the pharmacokinetics of propofol found that their concentration curves were described best by a three-compartment model [6–8]; and it has also been suggested that two-compartment models may be less accurate, particularly in estimating the initial volume of distribution [5].

Induction of anaesthesia by computer control was smooth and reliable, with no complaints of pain on injection. Intubating and operating conditions were good, with only a few patients needing supplementary volatile agents. It was easy to use the system, potentially leaving the anaesthetist more able to concentrate on all aspects of safe anaesthesia. Sudden changes in haemodynamic variables were not seen and arterial pressure decreased gradually during the infusion to reach a steady value in both groups. This differed markedly from the 32% reduction in systolic arterial pressure over the first 1 min which was seen following a 2-mg kg^{-1} single dose with a constant infusion at just over 6 mg kg^{-1} h^{-1} [15]. Waking was fast and predictable following the cessation of infusion.

To improve the rate at which the target concentration was reached, the computer model was used to adjust the infusion rate constants according to the results from the first eight patients. These new values were used in group 2 and resulted in a more rapid achievement of the predicted target. However, the mean blood concentrations did increase above the target value with time, in spite of an identical final infusion rate (which depends only on the clearance). The only other difference between the two groups was the introduction of intermittent positive pressure ventilation in group 2. The slightly increased blood propofol concentrations could be accounted for by reduced clearance caused by a decrease of liver blood flow associated with artificial ventilation. It is also possible that this increase resulted from a difference in redistribution of the drug, again possibly because of IPPV. However, it is unlikely to result from the changes made to the rate constants in group 2, because these mainly affected the rapid redistribution into compartment 2.

Although we achieved mean blood propofol concentrations close to the target in group 1, the variability of the concentrations about the mean reflects the numerous variables which contribute to the population kinetic statistics identified by Sheiner, Rosenburg and Marathe [16] and applied by Maitre and colleagues for alfentanil [17]. We do not yet have sufficient data to apply their statistical methods (NONMEM) to the evaluation of propofol kinetics under the conditions of continuous infusion.

We used venous blood sampling throughout because the pharmacokinetic data used for calculating the infusion rate were all derived from studies using venous sampling. During the initial phase when the concentration is increasing rapidly towards its target level, the timing of samples is most critical, and this may explain the slightly larger standard deviation at 2 min. Also during this period, the concentration in venous blood lags behind that in arterial blood and this was confirmed for propofol concentrations in one patient from another series when arterial and venous samples were taken simultaneously (unpublished). Thus the initial low venous values seen in our patients probably represent arterial blood concentrations nearer the predicted target value.

This study has demonstrated that it is possible rapidly to attain and maintain constant blood propofol concentrations using a computerized infusion system. It has also supported the hypothesis that avoiding large fluctuations in propofol blood concentrations results in more stable clinical conditions, and has provided the basis for further research into both improved regimens of manually controlled propofol administration, and possible pharmacokinetic interactions.

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PROPOFOL FOR INDUCTION AND MAINTENANCE OF ANAESTHESIA: COMPARISON BETWEEN YOUNGER AND OLDER PATIENTS

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Since the introduction of propofol a difference in its effects between young and elderly patients has become apparent. For instance, older patients have a more pronounced tendency toward arterial hypotension after the administration of equal amounts of propofol [1, 2]. This tendency toward hypotension has been demonstrated in older patients for a variety of hypnotic drugs. The occasional deleterious effect of a relatively excessive dose of thiopentone on haemodynamics in the elderly is familiar to every clinical anaesthetist. Although the mechanism for such an "increased sensitivity" is not completely understood, it possibly could be the result of a decrease or a change in plasma protein content, resulting in an increase in unbound drug fraction in the elderly patient compared with the younger. Also, the perfusion of the tissue compartments may have changed in the elderly in favour of the well perfused tissues.

On account of its rapid onset and short duration of effect, and because of a rapid complete recovery without hangover or rebound phenomena, propofol is likely to become used extensively for the induction and maintenance of anaesthesia for outpatient surgery. In the present study we compared the requirements for propofol for induction and maintenance of anaesthesia, and the recovery times and side effects of propofol in younger and older patients.

SUMMARY

The propofol requirements for the induction and maintenance of anaesthesia were compared in groups of younger and older patients. Side effects, influence on the cardiovascular system and recovery times were compared between 20 unpremedicated ASA I–III, 25–40-yr-old patients and 20 65–80-yr-old patients all scheduled to undergo elective surgery. After induction with propofol, anaesthesia was maintained with a continuous infusion of the drug. Vecuronium and fentanyl were administered as required. In the young group propofol 2.2 mg kg^{-1} *and in the elderly 1.7 mg* kg^{-1} *were needed for induction (*$P < 0.05$*). The maintenance doses were 10.0 mg* kg^{-1} h^{-1} *and 8.6 mg* kg^{-1} h^{-1}*, respectively (*$P < 0.01$*). Side effects were more pronounced in the younger patients. Influences on the cardiovascular system were definite, but mild. The younger patients awoke sooner: 7.8 v. 14.3 min (*$P < 0.01$*) after the discontinuation of the infusion of propofol.*

PATIENTS AND MATERIALS

Forty patients of both sexes, ASA classification I–III, admitted for surgery under general anaesthesia of an expected duration not exceeding 120 min, were included in the study. Approval of the hospital Ethics Committee was obtained for the study. All patients gave verbal informed consent to participate. Twenty patients were selected in the age range 25–40 yr (group A) and 20 patients of 65–80 yr (group B). Excluded from the study were pregnant patients, patients with severe obesity (weight more than 120% in relation to body height), patients receiving any medication

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possibly interfering with the anaesthetic (neuroleptic agents, tranquillizers or other psychopharmaceutic drugs), patients with a known allergy to propofol or its solvent (Intralipid), or patients with abnormal renal, hepatic or haemopoietic functions.

Premedication was avoided because of the risk of interference with the anaesthetic [3]. Before induction of anaesthesia an i.v. infusion of physiological saline solution was started in a vein in the forearm or dorsum of the hand. An electrocardiogram, lead 2, was continuously monitored and registered on a polygraph. Arterial pressure and heart rate were measured just before the induction of anaesthesia, at 1-min intervals for the next 10 min and, thereafter, at 2.5-min intervals, with the aid of an automatic non-invasive arterial pressure monitor. After baseline measurements of arterial pressure and heart rate had been obtained, anaesthesia was induced with propofol 1.5 mg kg^{-1}, administered over 20–40 s in a fast running i.v. infusion. At the same time an infusion of propofol 9 mg kg^{-1} h^{-1} was started to maintain anaesthesia. Induction time was defined as the period between start of bolus injection and disappearance of the eyelash reflex. If unconciousness was not attained after 1 min, additional propofol 20-mg boluses were given. As soon as unconciousness was attained a Relaxograph (Datex) was connected and calibrated. The neuromuscular blockade produced by administration of vecuronium bromide 0.1 mg kg^{-1} was measured at the adductor pollicis muscle. Fentanyl 1.5 μg kg^{-1} was given with the neuromuscular blocking drug. When muscle contraction had decreased by 90%, the trachea was intubated and artificial ventilation commenced with oxygen-enriched air (40% oxygen), to keep the end-tidal carbon dioxide partial pressure at 4.7–6 kPa. Intubation time was defined as the period between start of propofol infusion and completion of intubation.

Fentanyl 0.75–1.5 μg kg^{-1} was administered every 30 min. When very painful stimuli were expected, for example during orthopaedic surgery, additional 1.5-μg kg^{-1} doses were administered. Also, when arterial pressure or heart rate increased, or when the finger plethysmogram narrowed and there was no reason to expect insufficient hypnosis, additional fentanyl was preferred to propofol. Supplementary doses of vecuronium were administered according to the clinical need of the patient.

In patients in whom heart rate decreased to less than 55 beat min^{-1} during anaesthesia, atropine was administered i.v. to restore normal heart rate. Supplementary bolus doses of propofol 20 mg were given when considered necessary as determined by an increase in systolic arterial pressure as long as analgesia was adequate. When other signs of light anaesthesia were present, such as coughing, moving, hypersalivation, swallowing or chewing on the tracheal tube, epiphora or sweating, propofol 20 mg was given. If, during maintenance of anaesthesia, systolic arterial pressure decreased to less than 90 mm Hg, the rate of infusion of propofol was halved to 4.5 mg kg^{-1} h^{-1}. Maintenance time was defined as the period starting immediately after intubation until the end of infusion of propofol.

At the end of the operation neuromuscular blockade was antagonized, when necessary, with neostigmine and atropine in usual doses, as soon as recovery of block had passed 25%.

All events were recorded to enable comparison of induction time, intubation time, the induction dose of propofol and the total amount administered until intubation. Extubation time (time from end of infusion to extubation), awakening time (time from end of infusion to opening of eyes), and orientation time (time from end of infusion to orientation in time and place) were also compared for both groups. The percentage differences from pre-anaesthetic baseline values of arterial pressure and heart rate were calculated immediately and 3 min after intubation, as well as the lowest values before intubation, before surgery started and the highest and lowest values during surgery. Adverse effects occurring during induction, maintenance, early recovery and up to 24 h after surgery were recorded. The quality of induction was judged by two of the authors and an anaesthetic nurse confirmed the side effects noted at induction. Patients were asked about awareness during induction and maintenance, and their opinion of the anaesthetic.

The data were analysed statistically by Chi-square test, Mann–Whitney *U* test or Student's *t* test for paired data, as appropriate. $P < 0.05$ was considered to be significant.

RESULTS

Twenty patients were initially entered in each group. Two patients in group A were excluded because of exceeding the propofol infusion time of 120 min. In group B one patient had to be excluded for not fulfilling the age range criterion. This left 12 females and six males in group A and 6 and 13, respectively, in group B. Patient details are summarized in table I.

There was no significant difference in body weight or body height ($P > 0.05$). In general, the elderly patients belonged to a higher ASA class because of a significantly ($P < 0.01$) higher prevalence of concurrent diseases: three in group A *v.* 14 in group B. Seven patients in group B and three in group A were receiving drug therapy (ns). Four patients in group B were receiving a diuretic as management of hypertension (this drug was withdrawn the day before surgery). No patient was in receipt of beta-blockers. Surgical procedures comprised body surface (including herniotomies and laparoscopies), bones (including laminectomies) and intra-abdominal.

The induction time and dose of propofol, propofol utilization during maintenance of anaesthesia, calculated over both the period until withdrawal of the infusion and until opening of eyes (awakening), and the infusion times are given in table II, together with fentanyl maintenance doses.

Five of 18 patients in group A and 15 of 19 in group B ($P < 0.05$) lost the eyelash reflexes with the induction dose of 1.5 mg kg^{-1}. In group A the amount of propofol needed for induction and maintenance of anaesthesia was significantly higher than in group B ($P < 0.01$). Patients in group A more often showed signs of light anaesthesia, required additional propofol bolus more often and had fewer periods of excessive deep anaesthesia during maintenance (table III).

The amount of fentanyl required during the maintenance period was significantly less for group B than for group A (2.05 (SD 0.8) *v.* 3.08 (SD 1.4) μg kg^{-1} h^{-1}).

In the younger patients moving, muscular

TABLE I *Demographic data on the groups studied (mean (SD) [range]). Significant differences:* *P *< 0.05;* **P *< 0.01*

	Group A (n = 18)		Group B (n = 19)
Age (yr)	32.6 (4.8) [25–39]	**	71.1 (4.1) [66–80]
Body weight (kg)	69.3 (12.7) [47–94]		73.1 (12.7) [47–98]
Body height (cm)	170 (12) [151–193]		172 (10) [149–192]
ASA			
I	15	*	5
II	2		7
III	1	*	7
Surgical procedure			
Body surface	13		13
Bone	4		5
Intra-abdominal	1		1

TABLE II. *Comparison of the amounts of propofol and fentanyl supplied (mean (SD) [range]). Maintenance doses are calculated over the period until end of infusion or awakening.* **P *< 0.01*

	Group A		Group B
Propofol			
Induction dose (mg)	2.2 (0.4) [1.6–2.8]	**	1.7 (0.2) [1.6–2.2]
Intubation dose (mg kg^{-1})	3.6 (0.9) [2.2–5.9]	**	2.6 (0.4) [2.1–3.8]
Maintenance dose (mg kg^{-1} h^{-1})			
To end infusion	10.0 (1.3) [6.2–12.3]	**	8.6 (1.1) [6.4–10.9]
To open eyes			
Males + females	8.5 (1.3) [5.8–11.5]	**	6.9 (1.0) [3.9–7.9]
Males only	7.9 (1.2)		6.8 (1.1)
Females only	8.8 (1.2)		7.2 (0.5)
Fentanyl			
Maintenance dose (mg kg^{-1} h^{-1})			
To end infusion	3.08 (1.42) [0.0–5.79]	**	2.05 (0.80) [0.0–3.67]
To open eyes	2.56 (1.09) [0.0–4.37]	**	1.63 (0.62) [0.0–3.10]

hypertonicity and discomfort at the site of injection were observed at induction more frequently than in the older patients. The complete list of side effects is shown in table IV.

There was a tendency for intubation to be achieved faster in older patients (intubation time 4–8 min) than in younger patients (range 5–17 min). The intubation time of 17 min in one young patient was caused by calibration problems; exclusion of the results from this patient does not change the significance.

When asleep, all patients tolerated a face mask for the administration of oxygen-enriched air before tracheal intubation, and their lungs were remarkably easy to ventilate by hand. The time from start of induction to suitable operative conditions was 9.8 (2.2) min in group A and 7.6 (3.1) min in group B.

TABLE III. *Quality of anaesthesia during maintenance. Occ. = Occasional; Cont. = continuous.* *$P < 0.05$

	Group A			Group B		
	None	Occ.	Cont.	None	Occ.	Cont.
Periods of light anaesthesia	5	9	4	13*	5	1
Movement during surgery	10	7	1	18*	1*	0
Need for additional bolus	4	8	6	11*	7	1*
Excessive deep anaesthesia	16	2	—	13	6	—

TABLE IV. *Observed side-effects during induction, maintenance and early and late recovery in group A and group B.* *$P < 0.05$

	Induction		Maintenance		Early rec.		Late rec.	
	A	B	A	B	A	B	A	B
None	2	11*	10	17*	5	10	16	16
Pain on injection	10	2*	—	—				
Movement	4	1	2	—				
Hypertonicity	5	2	—	—				
Myoclonus	4	1	1	—				
Flush	1	—	1	—				
Hypersalivation	—	—	2	—				
Hiccup	—	1	2	1				
Other	2	1	1	1				
Nausea					4	4	—	3
Vomiting					2	2	—	3
Restlessness					5	5	—	—
"Euphoria"					5	4	—	—
Depressed					2	—	—	—
Headache					2	1	2	—
Other					4	2	—	—

TABLE V. *Comparison of times to induction and intubation, total infusion time, extubation time, awakening time and time to orientation (mean (SD) [range]).* *$P < 0.05$; **$P < 0.01$. †*Excludes upper limit of one anomalous patient (see text)*

	Group A		Group B
Induction time (s)	90 (30) [45–110]	**	57 (15) [35–100]
Intubation time (min)	7.4 (2.7) [5–17]	**	5.4 (0.9) [4–8]
Infusion time (min)	60.1 (26.6) [31–118]		73.1 (26.7) [35–118]
Extubation time (min)	6.6 (2.6) [2–11]	*	9.6 (5.6) [1–15]†
Awakening time (min)	7.8 (3.0) [2–14]	**	14.3 (9.9) [4–28]†
Orientation time (min)	9.8 (3.4) [4–17]	**	17.0 (11.0) [5–32]†

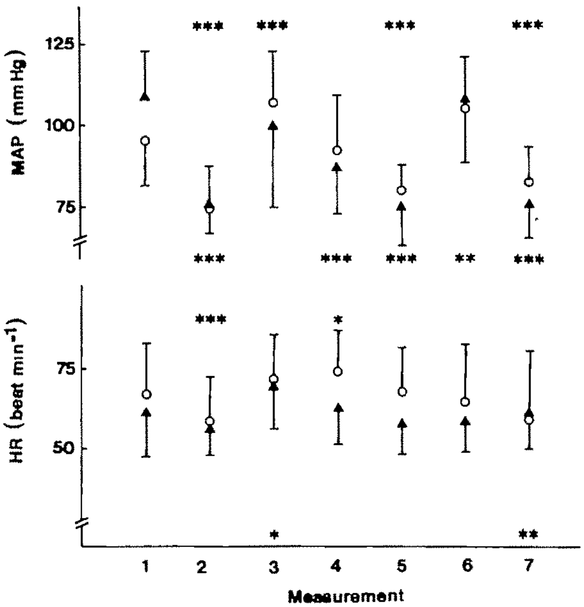

FIG. 1. Mean values for arterial pressure and heart rate at baseline conditions (1), lowest value before intubation (2), immediately after intubation (3), 3 min after intubation (4), lowest value before surgery (5), highest value during surgery (6) and lowest value during surgery (7). Differences from baseline values: $*P < 0.05$; $**P < 0.02$; $***P < 0.01$. ○ = Younger patients (25–40 yr); ▲ = older patients (65–80 yr).

Induction time, intubation time, total infusion time, extubation time, awakening time and orientation time are given in table V. Recovery in group A was faster than in group B ($P < 0.05$), but there was no significant difference in total infusion time. One patient in group B had longer recovery times for extubation, awakening and recovery (27, 49 and 55 min, respectively), but this patient received the highest fentanyl dose in group B in a total hip procedure which lasted 93 min.

None of the patients experienced awareness during induction or maintenance of anaesthesia.

Statistically significant changes in arterial pressure compared with baseline values were seen at all subsequent measurements (fig. 1), propofol causing a decrease in arterial pressure which was especially marked in group B. Smaller accompanying changes in heart rate were seen, with a tendency toward slower rates in group B. Individual percentage changes in arterial pressure from baseline values for groups A and B are reproduced in figure 2. In group A a systolic arterial pressure less than 90 mm Hg was noted in two patients before intubation. In three patients a pressure greater than 160 mm Hg was measured immediately after intubation. In group B seven patients had baseline systolic arterial pressures greater than 160 mm Hg. In five patients arterial pressures decreased to less than 90 mm Hg before intubation (one to less than 80 mm Hg). In five patients in group B arterial pressure greater than 160 mm Hg was recorded immediately after intubation.

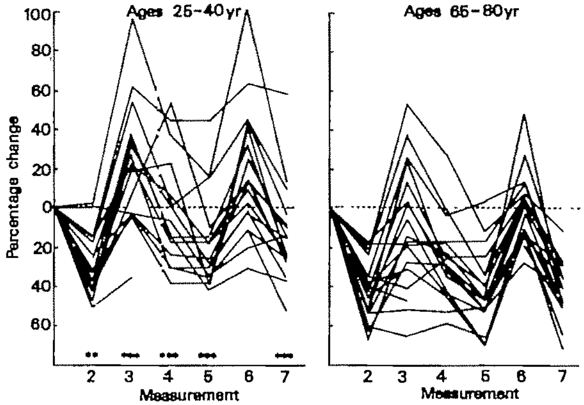

FIG. 2. Normalized percentage changes in arterial pressure from baseline values at the same measurement points as in figure 1. Statistical difference between means: $*P < 0.05$; $**P < 0.02$; $***P < 0.01$.

No patient suffered from any cardiovascular sequelae during and after recovery from anaesthesia.

DISCUSSION

Several investigators have demonstrated a difference in the amount of propofol needed for the induction of anaesthesia between younger and older patients [1, 2]. The induction dose of 1.5 mg kg^{-1} was chosen as that recommended in the literature for patients older than 65 yr [2, 4]. To enable comparison of induction requirements, doses for young and elderly must be the same, although we realized that it was possible that young patients would not lose consciousness after this dose. An age-related difference in requirement of propofol for maintenance has not previously been demonstrated.

Unfortunately, we introduced a possible bias to our results, with more females in group A. However, it has been observed that induction doses of propofol do not differ significantly between males and females [2], and Kay and co-workers [5] demonstrated comparable steady-state distribution volumes for males and females, and so we believe that our results for rate of propofol utilization are not influenced by sex differences. This is further supported by examination of the separated male and female requirements for maintenance drugs over the period until opening of eyes, which do not differ essentially from the male and female combined data (table II).

As could be expected from the higher incidence of concurrent diseases in the elderly, more patients in group B than in group A were in ASA classes II or III. In our experience, however, there is no predictive value of ASA class I–III in estimation of anaesthetic requirement. All patients were clinically fit for elective surgery. Some scored ASA III mainly because of chronic obstructive pulmonary disease or hypertension with ECG abnormalities, which is more an indication of cardiovascular instability than of requirement for hypnotic medication, at least in the patient population studied.

Homer and Stanski [6] found a significant decrease in initial volume of distribution for thiopentone with increasing age, based on the existence of a smaller central compartment, which would also result in higher initial serum concentrations. This may explain the smaller requirement for propofol for induction of anaesthesia in the elderly. Another reason for higher sensitivity to propofol in the elderly could be an increased free plasma fraction of propofol based on a small concentration, or a changed pattern, of plasma proteins. In man the protein-bound fraction is about 98%, while administration of fentanyl increases the free plasma fraction of propofol [7]. A smaller central compartment may also explain the lower requirement for maintenance doses in the elderly when short acting drugs are used.

There was a considerable and statistically significant difference between the groups in propofol requirements during maintenance of anaesthesia. Group A received a 16% greater maintenance dose over the period until the end of the propofol infusion, or 23% more until opening of the eyes. This difference is of even greater significance when one considers that group A also received significantly more fentanyl. Despite receiving more propofol and fentanyl, patients in group A were less deeply anaesthetized than those in group B. This suggests a fundamentally greater maintenance requirement for group A. Nevertheless, the utilization ranges remained within those described in a previous study in which age was not a selection criterion [8]. In that study, maintenance utilization rate was 10.0 (2.4) mg kg^{-1} h^{-1}, or 7.5 (2.2) mg kg^{1} h^{-1} if calculated until awakening (opening of the eyes). The age range of the subjects was 19–48 yr. A difference in incidence of movement during surgery between young and elderly patients receiving the same anaesthetic regimen has been described by Hilton, Dev and Major [9].

During maintenance of anaesthesia the amounts of fentanyl given were small: about 225 μg h^{-1} and about 150 μg kg^{-1} for a 70-kg patient in groups A and B, respectively. An analgesic effect of propofol has been demonstrated [10] which, if an inherent property of the drug, is of special interest for day-case anaesthesia.

The combination of propofol, fentanyl and vecuronium bromide offers stable anaesthesia with a tendency toward low-normal heart rates. Although substantial changes in arterial pressures were noticed, these rarely exceeded normal ranges. The more pronounced decrease in arterial pressure in group B was probably influenced by the five patients receiving diuretic and other antihypertensive drugs causing a relative hypovolaemia. In addition, the greater propofol plasma concentration alluded to above will produce more intense effects on the cardiovascular system. The pressor reflex decreases with increasing age, also.

All patients became unconscious within times comparable to those reported by other investigators. The prolonged intubation time we found in young patients compared with the older may be explained by the relatively small induction dose of propofol used. Increasing the induction dose to 2.0–2.5 mg kg^{-1} accelerates induction [8]. Application and calibration of the neuromuscular transmission monitor caused some delay and thus also prolonged intubation times in general.

Recovery from anaesthesia, measured as time to awakening and as time to orientation, was more variable in group B than in group A.

Since the introduction of propofol in Cremophor solution, pain on injection has been the most striking side effect of the drug [3, 11]. With emulsified propofol the incidence and severity of pain on injection have decreased. Nevertheless, pain was experienced in both groups in our study, significantly more pronounced in the younger group. A decreasing sensitivity of the peripheral nervous system and a lesser irritability of the vasculature in the elderly patient may explain this difference. In this study we administered fentanyl only after the patient had lost consciousness. In routine clinical practice fentanyl or another opioid will usually be administered earlier and may thus decrease the incidence of pain on injection of propofol. Premedication may also reduce the experience of pain on injection.

The incidence of nausea and vomiting was similar to that in other studies with propofol, but lower than that in our experience with other anaesthetics, especially etomidate [12, 13].

Other side effects of propofol were of minor clinical importance. Although eight patients in group A and six in group B had symptoms of emotional lability, these were of short duration—less than 30 min—and were considered as harmless emergence phenomena.

None of the patients reported awareness after having fallen asleep. Most patients were satisfied with the induction, although two patients would not have the same anaesthetic again because of pain on injection and one patient because of feeling too awake in the postoperative period.

In summary, this study showed that younger patients need considerably more propofol than patients older than 65 yr during induction and maintenance of anaesthesia, when the drug is used as a total i.v. anaesthetic. Propofol provided adequate and easily controllable anaesthesia, with rapid and uneventful recovery in elderly patients. Although younger patients required higher doses of both propofol and fentanyl, recovery was nevertheless more rapid. Pain on injection was less pronounced in the elderly.

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EARLY CORTICAL AUDITORY EVOKED RESPONSE IN ANAESTHESIA: COMPARISON OF THE EFFECTS OF NITROUS OXIDE AND ISOFLURANE

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SUMMARY

Previous studies showing graded changes in the early cortical waves Pa and Nb of the auditory evoked response (AER) with increasing concentration of volatile anaesthetic agents demonstrated high amplitudes of these waves in the period immediately following induction of anaesthesia and tracheal intubation, when the patient breathed nitrous oxide alone. These high amplitude waves were not consistent with extrapolation of the data or observations of patients under steady-state nitrous oxide anaesthesia. In order to discriminate between effects in the period immediately following induction of anaesthesia and tracheal intubation, and effects caused by nitrous oxide alone, a randomized cross-over study was performed. Eight patients breathed either nitrous oxide or isoflurane at 0.6 MAC for three consecutive 10-min periods following intubation and before surgery. The amplitudes of Pa and Nb were significantly less for isoflurane with respect to the same MAC fraction of nitrous oxide in all periods, but for both agents the amplitudes were significantly greater in the 10 min following intubation than in subsequent periods, presumably as a result of stimulation.

Previous studies on depth of anaesthesia have shown graded changes in the auditory evoked response (AER) in patients anaesthetized with increasing concentrations of volatile anaesthetic agents [1,2]. In these studies the amplitudes of the early cortical waves, Pa and Nb, decreased progressively as the concentrations of halothane, enflurane and isoflurane were increased. However, when observed several minutes after induction of anaesthesia and before the administration of the volatile agent, the amplitudes of these early cortical waves appeared frequently to exceed their pre-anaesthetic values. In this period, anaesthesia was provided solely by nitrous oxide and the declining concentration of the induction agent, thiopentone.

From these data it is not possible to differentiate between the effects of nitrous oxide alone, which could possibly have had an excitatory effect, and those effects produced by the potentially stressful sequence (induction of anaesthesia and tracheal intubation) that preceded it. Recent studies have shown that the depression of the early cortical AER by anaesthetic agents may be reversed partially by the stimulus of surgery [3].

We have conducted a cross-over study to examine the effects on these AER waves of the period immediately after induction and tracheal intubation in patients anaesthetized with equal MAC (minimal alveolar concentration) fractions of either nitrous oxide or isoflurane.

METHODS

Patients and anaesthesia

We studied eight patients (ages 38–49 yr; ASA I or II) undergoing major general or gynaecological abdominal surgery. The patients consented to the measurement of AER during 30 min of anaesthesia before surgery; the study was approved by the hospital Ethics Committee.

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TABLE I. *Experimental design for within subject comparison between nitrous oxide (N_2O) and isoflurane (ISO). Two patients in each sequence. Periods were consecutive, and of 10 min duration*

Sequence	Period 1	Period 2	Period 3
1	ISO	N_2O	N_2O
2	N_2O	ISO	N_2O
3	ISO	N_2O	ISO
4	N_2O	ISO	ISO

Each patient was premedicated with morphine 10–15 mg and atropine 0.6 mg, or papaveretum 15–20 mg and hyoscine 0.3–0.4 mg, i.m. 1 h before induction of anaesthesia with thiopentone 2–4 mg kg^{-1}. Intubation of the trachea was facilitated by either pancuronium or vecuronium 0.1 mg kg^{-1} and mechanical ventilation was adjusted to maintain an end-tidal $P\text{CO}_2$ of 4.5–5.0 kPa (Hewlett-Packard 47210A capnometer). Following tracheal intubation, the inspired gas mixture was adjusted to produce the required end-tidal concentrations (60–65 % nitrous oxide or 0.65–0.75 % isoflurane), as measured by mass spectrometer (Medishield MS2, calibrated by volumetrically prepared gas samples). These concentrations were chosen to give a fraction of approximately 0.6 MAC [4]. The anaesthetic administered was changed in each of the eight patients in three consecutive 10-min periods randomized as shown in table I.

Overpressure was used to produce rapidly the required end-tidal concentrations of the chosen agent; within 5 min, it was possible to have both stable end-tidal values and residual concentrations of the previous agent less than 5 % of their original value.

Systemic arterial pressure and heart rate were recorded every 2.5 min throughout the procedure using a Datascope automatic recorder. Nasopharyngeal temperature was recorded after tracheal intubation, and at the end of the study period.

Clinical assessment of the adequacy of anaesthesia was carried out during the study by an anaesthetist (not participating in the study) who supervised the patient. After surgery, patients were seen by this anaesthetist, who noted any volunteered recall of events during the procedure.

Recording the auditory evoked response

The technique has been described in detail previously [5]. In the present study a purpose built EEG amplifier was used in place of the modified Specialized Laboratory Equipment 10/8 polygraph. The gain and filter characteristics were the same (gain 100 dB; frequency response 25–3600 Hz). Clicks (75 dB above the average auditory threshold) were administered binaurally through headphones at a rate of 6 per second. The EEG was recorded using silver–silver chloride electrodes on the vertex and inion and was amplified and stored on an FM tape recorder. The AER was analysed off-line using a Datalab DL 4000 averager, to display the average of the response to 2048 clicks, during the last 5.7 min of each period when the end-tidal values were stable. For the early cortical waves Pa and Nb, latency and amplitude were measured. The nomenclature of these waves has been discussed previously [5].

Statistical analysis

Analysis of variance was used to compare the agents used and the periods during which the agents were administered, and to determine if there was an interaction between the effect of the drug and the period in which it was given. Statistical significance was assigned at the 5 % level.

RESULTS

Auditory evoked response (table II)

Nitrous oxide v. *isoflurane*. The effect of one sequence of administration is shown in figure 1. The change from nitrous oxide to isoflurane produced a marked reduction in amplitude and increased in latency of the early cortical waves, Pa and Nb. These changes were reversed partially by the sebsequent re-administration of nitrous oxide.

Analysis of the results for all eight patients showed large and significant decreases in the amplitude of the early cortical waves Pa ($P < 0.001$) and Nb ($P = 0.003$) for isoflurane compared with nitrous oxide, irrespective of the period administered. Latencies for both waves were increased when the patients received isoflurane; the change for Pa was significant ($P < 0.05$).

The effect of period. The amplitudes of waves Pa and Nb were significantly greater for both agents in the initial period immediately after tracheal intubation, compared with the two subsequent periods. The latencies were not affected significantly by the period. There were no significant interactions between drug and period.

The major effects were on the amplitudes of Pa and Nb. These are seen for one patient in figure 1 and are illustrated for the complete study in figure 2 for Pa amplitude, showing the consistently greater amplitude depression with 0.6 MAC isoflurane than with nitrous oxide irrespective of period, and the greater amplitudes seen in the first period, following tracheal intubation.

Cardiovascular variables

Arterial pressure and heart rate decreased significantly following the initial period, as would be expected in the absence of surgical stimulation. Systolic arterial pressure was slightly but significantly lower ($P < 0.001$), and heart rate higher ($P = 0.02$) in association with the adminstration of isoflurane compared with nitrous oxide.

In all patients temperatures remained within the range 36.0–37.5 °C during the period of investigation.

The patients appeared to be anaesthetized adequately during the period of the study (without any other stimulation), and no patient volunteered recall of any events during anaesthesia.

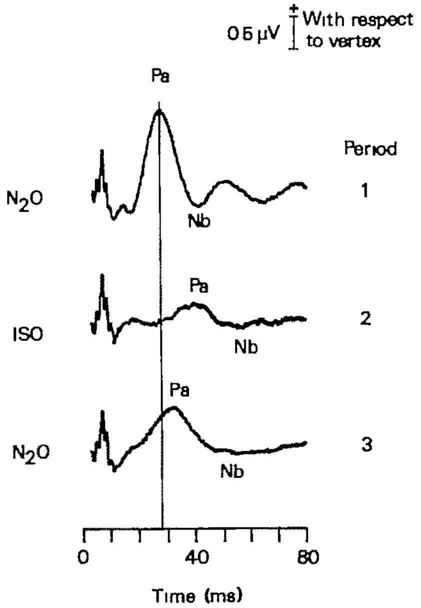

FIG. 1. Early cortical AER recordings in one patient, showing the progression from nitrous oxide (N_2O) anaesthesia following induction and intubation to isoflurane (ISO), and back to nitrous oxide.

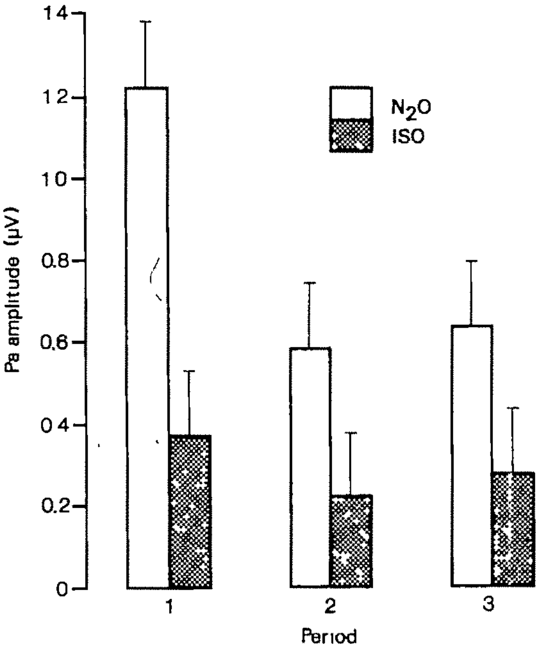

FIG. 2. The amplitudes of the early cortical AER wave Pa (SEM bars based on the pooled within-subject residual error term in the analysis of variance), for each of three consecutive 10-min periods following tracheal intubation, in eight patients receiving isoflurane (ISO) or nitrous oxide (N_2O).

TABLE II. *Analysis for four AER variables with respect to period (see table I) and drug (nitrous oxide (N_2O) or isoflurane (ISO)). Negative values represent reductions of latency or amplitude when going from the first to subsequent periods, or when changing from isoflurane to nitrous oxide*

	Differential effects					
	Period 1 v. 2 and 3			Drug: ISO v. N_2O		
Variable	Mean change	SEM	*P*	Mean change	SEM	*P*
Latency (ms)						
Pa	4.88	2.43	0.07	−8.25	2.52	0.006
Nb	7.00	3.79	0.10	−8.09	3.93	0.06
Amplitude (µV)						
Pa	−0.37	0.11	0.006	0.54	0.11	< 0.001
Nb	−0.41	0.10	< 0.001	0.38	0.10	0.003

DISCUSSION

The results show that nitrous oxide has a quantitatively different effect on the auditory evoked response from that of isoflurane when each is administered at 0.6 MAC. In particular, reductions in amplitude and increases in latency of the early cortical waves Pa and Nb in both periods 2 and 3 compared with period 1, were significantly less with nitrous oxide. For both agents the early cortical amplitudes were greater in period 1 (the 10 min following induction of anaesthesia and intubation of the trachea) than in the subsequent 20 min when the responses remained lower and stable, even though the end-tidal concentrations of the anaesthetic agents were the same in all three periods. The combination of both the effects demonstrated—of period, and of nitrous oxide—may explain the initially high Pa and Nb amplitudes seen in previous studies.

The advantage of the design of this study, using three periods rather than the more usual two periods for comparison of the two agents, was that interaction between drugs and periods could be tested against within-subject variability, rather than between-subject variability, which is usually much greater [6]. Using this design, it was possible to conduct the necessary within-patient crossover, during the 30 min of anaesthesia time before the start of surgery. Thirty minutes is the maximum extension time for anaesthesia research permitted by the hospital Ethics Committee.

In both the second and third periods, the degree of depression of amplitude of Pa and Nb in this study was similar to that in anaesthetized patients in previous studies [1, 2], in which combinations of various volatile agents and nitrous oxide were used. We chose to compare nitrous oxide with isoflurane, because earlier studies have shown that the effects of the various volatile agents on the early cortical AER were similar and isoflurane, unlike halothane, could be given safely to all patients. However, in this present study, isoflurane at 0.6 MAC was exerting a greater effect than the equivalent MAC combination (nitrous oxide plus isoflurane) in the previous study [2]. It is interesting to note that, in order to achieve the required end-tidal isoflurane concentrations in this study, inspired concentrations of at least twice the end-tidal value were needed throughout the 10- or 20-min periods. We should question, therefore, the assumption of McMenemin and Parbrook [7] that the alveolar concentration should equal 60% of the inspired concentration after 20 min, and would recommend rapid response end-tidal gas analysis for studies of this type.

The effect of nitrous oxide on the auditory evoked responses has been studied extensively. Lader and Norris [8] demonstrated, in man, reductions in the amplitude of the AER by inspired concentrations as low as 12%. More recent work has demonstrated graded changes in AER amplitudes, with various concentrations up to 50% [9, 10].

The technical difficulties of recording the early cortical AER in the operating theatre [11] have ensured that it has not been studied extensively in relation to the inhalation anaesthetic agents. However, several studies [1–3, 12, 13] have demonstrated that it shows promise as a monitor because significant changes are seen in response to increasing concentrations of both inhalation and i.v. anaesthetic agents.

With the exception of the determination of MAC values in man, very few studies have been performed on volatile anaesthetic agents without the use of nitrous oxide as a carrier gas. However, we have shown that equivalent MAC fractions of nitrous oxide and isoflurane are not equipotent as indicated by the AER. This may cast some doubt on the current practice of adding MAC fractions to determine the potency of a mixture of volatile agent and nitrous oxide.

There is no reason to suppose that the dose–response curves of the AER with volatile anaesthetic agents should be similar. Our results support the comments of Eger [14] on the work of Frumin [15] and others, suggesting that the relative anaesthetic potency of nitrous oxide in clinical concentrations, from its MAC-awake value, was lower than that expected by comparison with other agents. The anomalous properties of nitrous oxide may result from both sympathetic activation, and the high analgesic component of the drug's activity.

Estimations of MAC depend on the resultant of both hypnotic and analgesic activities in response to surgical stimulus. In this study, the patients were not stimulated surgically, and only the hypnotic effects of the two drugs were tested. Thus our results may be explained by the hypothesis that we may have compared a drug good with analgesic but weak hypnotic properties against one with poor analgesic but good hypnotic actions. Further studies are necessary to demonstrate if the early cortical AER amplitude depression is solely a measure of hypnosis during anaesthesia.

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Br. J. Anaesth. (1989), **62**, 66–69

ADRENAL CORTICAL RESERVE IN PATIENTS UNDERGOING MUSCLE BIOPSY FOR MALIGNANT HYPERTHERMIA SCREENING

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SUMMARY

Stress has been suggested as a factor involved in the development of a malignant hyperthermia (MH) reaction. This study has compared the hormonal response of a group of patients susceptible to MH (MHS), with that of a control group, during diagnostic muscle biopsy under general anaesthesia. Preoperative adrenal cortical reserve was assessed using the Short Synacthen Test (SST). There was no significant difference between the groups in their hormonal response to the procedure, both groups showing a peroperative reduction in plasma cortisol concentration from an initially high value, and the SST was within accepted normal limits for both groups. It was concluded that patients susceptible to MH have normal adrenal cortical reserve and responded normally to the psychological and surgical stress encountered during this study.

Stress has been stated to be a factor involved in the development of a malignant hyperthermic (MH) episode [1–3] although studies in this department have failed to identify significant differences between MH susceptible (MHS) patients and normal controls when exposed to crescendo exercise [4], cooling [5] and continuous exercise [6]. However, a reduction in plasma cortisol has been shown following induction of anaesthesia, without a subsequent increase with the surgical stimulus of diagnostic muscle biopsy [7]. The present study was undertaken to compare this reduction in plasma cortisol in MHS patients and control individuals and relate it to the preoperative adrenal cortical reserve, in addition to indicators of the stress response, including disturbance in carbohydrate metabolism, and plasma prolactin concentrations [8, 9].

Adrenal cortical reserve was assessed using the Short Synacthen Test (SST) [10]. The SST was chosen because the hormonal disturbance is brief, as ACTH is destroyed in plasma within a few minutes [11], thus enabling the same patient to be studied on the following day with little or no interference with hormonal status.

PATIENTS AND METHODS

The patients included in the study were aged 15–50 yr, taking no drugs, and having no medical problems. They were attending for a diagnostic muscle biopsy to determine MH susceptibility [12] because they either had experienced a potential MH reaction to anaesthesia or had a relative who was known to be MHS. All patients gave informed consent, and the study was approved by the Leeds Eastern Health Authority Ethics Committee.

The SST was undertaken on the afternoon before the day of surgery. Patients were allowed a light lunch. Venous blood was sampled from an indwelling cannula which was inserted using local anaesthesia. Thirty minutes later, 5 ml of blood was taken into a plain tube for measurement of baseline cortisol concentrations. An i.v. injection of Synacthen 250 µg was given, and further samples were taken for plasma cortisol measurement as 15, 30, 45, 60 and 90 min.

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The following morning patients were prepared for theatre and given a standard anaesthetic of incremental i.v. thiopentone and fentanyl while breathing Entonox spontaneously from a halothane-free circuit [12].

During operation, 20-ml venous blood samples were taken from an i.v. cannula, at the following times: before induction of anaesthesia, in the anaesthetic room; during the muscle biopsy, approximately 15 min after induction; 30 min after termination of the anaesthetic, in the recovery room; 2 h after termination of the anaesthetic. Sample tubes were placed in melting ice, centrifuged within 1 h and the plasma or serum cooled to −80 °C for storage and later assay for cortisol, glucose, insulin and prolactin. Creatinine kinase (CK) was measured in the preoperative sample only.

Cortisol was measured using the Abbott TDX fluorescent polarization method and prolactin was measured using an enhanced radioimmunoassay. Patients were assigned to MHS or control (MHN) groups on the basis of the result of the muscle biopsy according to the European MH Group Protocol [13, 14]. Student's *t* test was used to determine the significance of differences between the group means. Values are given as mean (SEM).

RESULTS

There were nine patients in the MHS group and 17 in the control (MHN) group. Both groups were comparable for age, height, weight, duration of operation and doses of fentanyl and thiopentone used (table I).

From the results of the SST (fig. 1), there was no difference between the two groups. There was no difference between the groups in perioperative cortisol concentrations, which showed a consistent and progressively downward trend during the period of study (fig. 2). Prolactin concentrations

TABLE I. *Mean (SD) demographic data, total doses of thiopentone and fentanyl, and duration of operation in the two groups*

	MHS group		Controls	
n	9		17	
Age (yr)	25	(9)	33	(10)
Height (cm)	166	(11)	163	(19)
Weight (kg)	65	(11)	65	(11)
Surgical time (min)	23	(2)	27	(6)
Fentanyl (μg kg^{-1})	3.08	(0.40)	2.86	(0.05)
Thiopentone (mg kg^{-1})	9.8	(1.2)	8.9	(2.0)

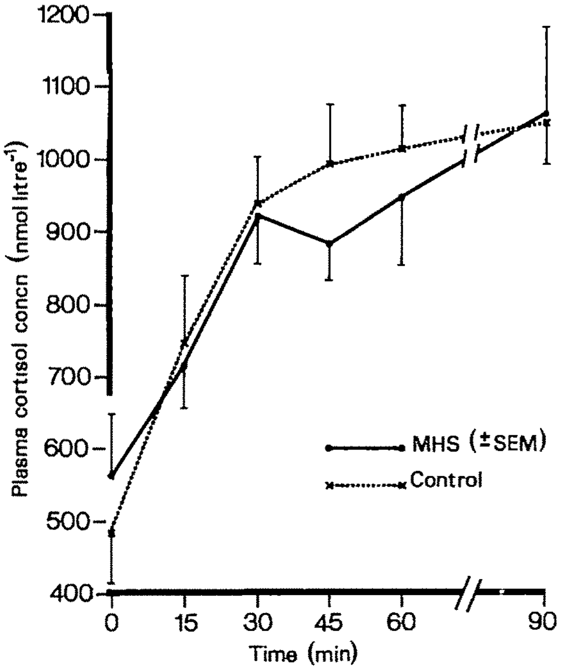

FIG. 1. Mean (SEM bars) plasma cortisol concentrations in MH susceptible (●——●) and normal (× --- ×) subjects following the administration of Synacthen 250 µg.

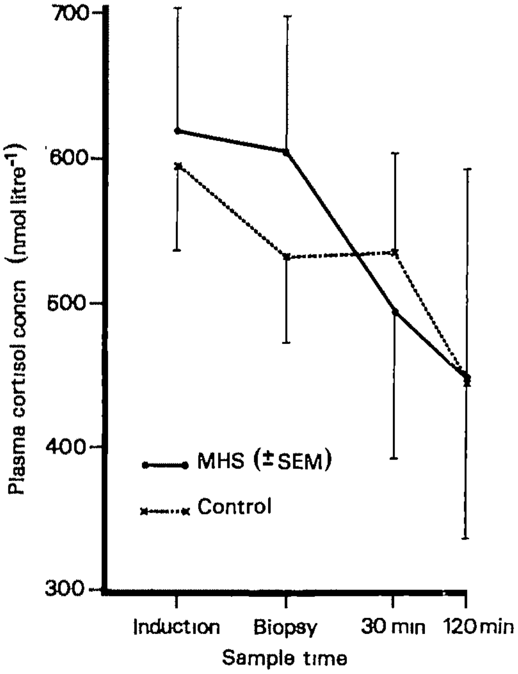

FIG. 2. Mean (SEM bars) perioperative cortisol concentrations in MH susceptible (●——●) and normal (× --- ×) subjects.

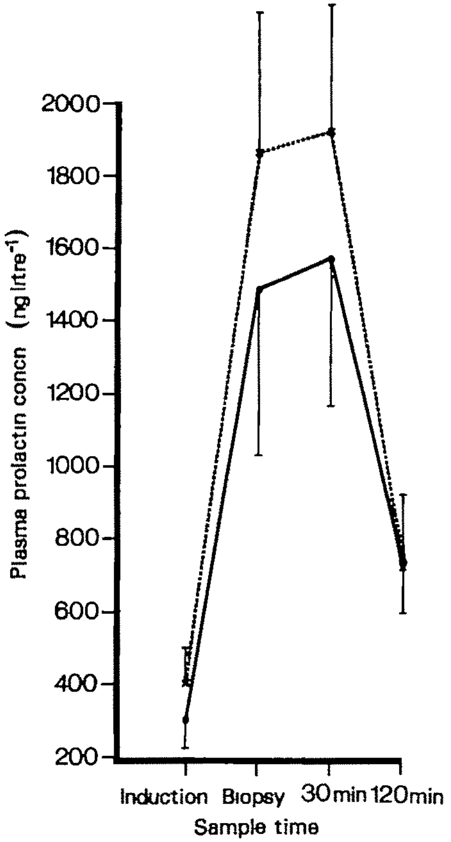

FIG. 3. Mean (SEM bars) perioperative prolactin concentrations in MH susceptible (●——●) and normal (× --- ×) subjects.

increased during surgery, followed by a decrease after surgery towards preoperative concentrations (fig. 3). Preoperative CK concentrations were not significantly different between the MHS and control groups, at 290 (204) iu litre^{-1} and 171 (89) iu litre^{-1}, respectively. Glucose:insulin ratios remained at induction values throughout the study period in both groups.

DISCUSSION

Both control and MHS groups had normal SST values, indicating that MHS patients have a normal adrenocortical reserve, capable of maximal cortisol production in response to ACTH stimulation. Longer tests of adrenocortical function were not used as they may have interfered with the hormonal status of the patient on the following day when surgery was performed. This does not, however, exclude the possibility of a difference with prolonged stimulation. However, neither group demonstrated the expected increase in cortisol production in response to the physical stress of a surgical procedure [8, 15]. It is possible that diagnostic muscle biopsy is not sufficiently traumatic to cause an increase in cortisol production. However, both groups had relatively high plasma cortisol concentrations before induction of anaesthesia, and it is well documented that preoperative psychological stress and anxiety can cause increased plasma cortisol concentrations in a direct relationship to anxiety [16, 17]. These patients were unpremedicated to avoid pharmacological contamination of the biopsy specimen, and their preoperative fear of anaesthesia may have been greater than average because of a personal or family history of anaesthetic tragedy. These factors may have increased the preoperative cortisol response to psychological stress to a degree greater than that expected to be caused by the surgical trauma. This would explain the gradual but consistent decline in cortisol concentrations following induction. Preoperative cortisol concentrations were less than those induced during SST, indicating there was still reserve adrenal function. The peroperative decline, therefore, did not indicate adrenal failure, but rather a decrease in overall stress.

Prolactin concentrations showed a marked increase on commencement of surgery with a similar reduction some time after surgery. It has been reported that stress can produce an increase in prolactin, despite its theoretical suppression by the increased growth hormone concentrations seen in both physical and psychological stress [18]. However, the operative increase in the present study was taken as an indication of the sensitivity of prolactin as a measure of physical, as opposed to psychological, stress [9].

The lack of any difference in CK measurements between the two groups confirms previous studies suggesting that it is not a useful measurement for the screening of MH [19, 20].

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Br. J. Anaesth. (1989), 62, 70–76

OXYGEN CONSUMPTION AND CARBON DIOXIDE ELIMINATION IN INFANTS AND CHILDREN DURING ANAESTHESIA AND SURGERY

S. G. E. LINDAHL

SUMMARY

Oxygen consumption ($\dot{V}O_2$, ml min^{-1}) and carbon dioxide elimination ($\dot{V}CO_2$, ml min^{-1}), minute ventilation ($\dot{V}E$), tidal volume (V_T), rate of ventilation (f) and end-tidal carbon dioxide concentration (E'_{CO_2}%) were measured in 38 infants and children (body weights 3.6–25 kg). Four children (body weight < 5 kg) had congenital heart malformations and were studied during controlled mechanical ventilation, whereas the remainder (n = 34) who were healthy, breathed spontaneously. Anaesthesia was maintained with oxygen in air ($F_{I_{O_2}}$ 0.45) and halothane through a non-rebreathing circuit. Minute ventilation was measured by pneumotachography, E'_{CO_2} with an in-line infra-red carbon dioxide meter and gas concentrations with a mass spectrometer. There were no differences in $\dot{V}O_2$ and $\dot{V}CO_2$ between children with and without heart disease. $\dot{V}O_2$ was related to body weight by the equation: $\dot{V}O_2 = 5.0 \times kg + 19.8$ (r = 0.94) and $\dot{V}CO_2$ to body weight by the equation: $\dot{V}CO_2 = 4.8 \times kg + 6.4$ (r = 0.94). There were no differences between $\dot{V}O_2$ or $\dot{V}CO_2$ before and after the start of surgery. In 11 of 21 patients weighing less than 10 kg, a reduced $\dot{V}CO_2$ was noted, giving respiratory quotients of less than 0.7. It is speculated that this age-dependent variation of $\dot{V}CO_2$ may result from partial inhibition of lipolysis in brown adipose tissue produced by halothane.

Oxygen consumption ($\dot{V}O_2$) and carbon dioxide elimination ($\dot{V}CO_2$), expressed on a weight basis, are greater in younger than in older, awake children [1–3]. However, during halothane anaesthesia, $\dot{V}CO_2$ correlates poorly with weight in young, spontaneously breathing infants of less than 10 kg [4, 5]. This discrepancy was found also by Nightingale and Lambert during mechanical ventilation in children, and they stated that $\dot{V}CO_2$ was unpredictable in infants weighing less than 10 kg [6]. These studies [4–6] showed an unpredictable $\dot{V}CO_2$ in spite of different measurement and anaesthetic techniques and mode of ventilation. It seems unlikely, therefore, that such factors are responsible for the changeable $\dot{V}CO_2$ observed in anaesthetized infants. However, it does suggest that metabolic variations may occur in anaesthetized infants.

The aim of the present study was to measure $\dot{V}CO_2$ and $\dot{V}O_2$ simultaneously in infants and children anaesthetized with halothane and to determine normal values for $\dot{V}O_2$ and respiratory quotient (RQ) both before and during surgery.

PATIENTS AND METHODS

We studied 38 children aged between 1 day and 7 yr, with body weights in the range 3.6–25 kg. All patients were fasted for at least 4 h before induction of anaesthesia. Four children weighing 4.9, 3.8, 3.7 and 3.6 kg had congenital heart disease (ASA Classes II, III) and their lungs were ventilated mechanically before and during surgery. These patients were scheduled to undergo repair of total anomalous pulmonary venous drainage, truncus arteriosus, Type I, large ventricular septal defect or transposition of the great arteries. The remainder 34 patients (age range 20 days to 7 yr, weight range 3.6–25 kg) were scheduled to undergo elective, general, urological or orthopaedic surgical procedures and had no signs of cardiorespiratory disease (ASA class I).

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The study was approved by the Institutional Review Board at the Mayo Clinic and parental consent to the study was given in each case.

Anaesthesia

Premedication was not used. Anaesthesia was induced with halothane and nitrous oxide in oxygen ($F_{I_{O_2}}$ 0.5). In non-cardiac patients, the trachea was intubated without the use of neuromuscular blockade. In cardiac patients, pancuronium bromide 0.1 mg kg^{-1} was used to facilitate tracheal intubation. Cuffed tracheal tubes (Mallinckrodt) were used to ensure an airtight connection. Anaesthesia in cardiac patients involved a Servo-ventilator 900 B with a rate of 30 cycles min^{-1} and ventilation volumes adjusted to produce an arterial carbon dioxide tension of approximately 4 kPa. Anaesthesia was maintained with fentanyl up to 40 µg kg^{-1} with a mean (SD) end-tidal halothane concentration of 0.26 (0.10)% in oxygen and air ($F_{I_{O_2}}$ 0.5). Non-cardiac patients were allowed to breathe spontaneously halothane 0.82 (0.17)% (mean value of end-tidal halothane concentration before surgery) in oxygen and air ($F_{I_{O_2}}$ 0.45) through a non-rebreathing anaesthesia circuit (Hans-Rudolph valve 2210B, deadspace 2.3 ml). MAC values for non-cardiac children were corrected for age according to Gregory, Eger and Munson [7] in children older than 6 months of age and according to Lerman and colleagues [8] in the younger. A heated humidifier was positioned in the inspiratory limb.

An infusion of 5.0% dextrose 3.6 ml kg^{-1} h^{-1} was given during the procedure, up to the time of measurements. In all patients, heart rate was recorded with an ECG, pulse rate and oxygen saturation with a pulse oximeter (Nellcor or Ohmeda) and systemic arterial pressure with a non-invasive oscillometric technique (Dinamap). Invasive arterial pressures were recorded in cardiac patients.

Measuring apparatus

An in-line infra-red capnometer (Hewlett-Packard 14360A) and a pneumotachograph (Fleisch Nos 00 and 0) were placed in the apparatus deadspace in order to confirm that ventilation was steady at the time of measurements. The deadspace of the system was 5 ml with Fleisch No. 00 and 8 ml with Fleisch No. 0, measured by water displacement. The inspiratory and expiratory resistances of the measuring apparatus were 14 cm H_2O $litre^{-1}$ s^{-1} for Fleisch No. 0 and 18 cm H_2O $litre^{-1}$ s^{-1} for Fleisch No. 00 at a flow of 6 litre min^{-1}. Minute ventilation ($\dot{V}_E$) was measured by electrical integration of the flow signal from the heated pneumotachograph and a differential manometer (Microswitch, Honeywell, 170PC). The Fleisch No. 00, used in patients weighing less than 6 kg, was linear for flows up to 8 litre min^{-1} and the Fleisch No. 0, used for heavier patients, was linear up to 18 litre min^{-1} The capnometer, which was positioned between the pneumotachograph and the valve, had a response time of 190 ms and an end-tidal plateau was identified in all patients. The capnometer confirmed also that rebreathing did not occur in any of the children. Air flow, $\dot{V}_E$ and end-tidal carbon dioxide concentrations were recorded on a six-channel recorder (General Scanning, R S6-5P) together with oesophageal, axillary, gas and room temperatures.

$\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ were measured over a 4-min period. Expired gas was collected in a Douglas bag (Neoprene). The bags used kept the gas concentration inside the bag constant for at least 10 min and no carbon dioxide diffusion was detected. Inspired gas concentrations were determined in duplicate (only variations in the second decimal place were accepted) by a mass spectrometer (Perkin–Elmer, Medical Gas Analyzer, MGA 1103). Mean expired concentrations of oxygen ($F\bar{E}_{O_2}$), nitrogen ($F\bar{E}_{N_2}$) and carbon dioxide ($F\bar{E}_{CO_2}$) were measured immediately by the same mass spectrometer at the end of the collection. The volume of gas in the bag (gas collection $\dot{V}_E$) was measured by a calibrated 3-litre syringe.

Calculations

Deadspace ventilation ($\dot{V}_D$), deadspace ratio (V_D/V_T), alveolar ventilation ($\dot{V}_A$), $\dot{V}_{CO_2}$, $\dot{V}_{O_2}$ and RQ were calculated according to the following formulae:

$$\dot{V}_{CO_2}\ (\text{ml min}^{-1}) = (\text{gas collection } \dot{V}_E) \times (F\bar{E}_{CO_2} - F_{I_{CO_2}})$$

$$\dot{V}_{O_2}\ (\text{ml min}^{-1}) = \left(\frac{F\bar{E}_{N_2}}{F_{I_{N_2}}} \times F_{I_{O_2}} - F\bar{E}_{O_2}\right) \times (\text{gas collection } \dot{V}_E)$$

$$\text{RQ} = \frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}}$$

$$\dot{V}_D' = \dot{V}_E - \dot{V}_A' - \dot{V}_D^{app}$$

$$V_D'/V_T = \frac{\dot{V}_D'}{\dot{V}_E}$$

$$\dot{V}\text{A}' = \frac{\dot{V}\text{CO}_2 \cdot P_\text{B}}{P\text{E}'_{\text{CO}_2}}$$

where $P\text{E}'_{\text{CO}_2}$ = end-tidal carbon dioxide tension, P_B = atmospheric pressure, $F\text{I}_{\text{N}_2}$ = inspired nitrogen fraction, $F\text{I}_{\text{O}_2}$ = inspired oxygen fraction. $\dot{V}\text{D}^{\text{app}}$ = apparatus deadspace. The superscript ′ indicates that $\dot{V}\text{A}$, $\dot{V}\text{D}$ and $V\text{D}$ were calculated non-invasively from $P\text{E}'_{\text{CO}_2}$ [9]. All gas volumes were corrected to standard temperature and pressure dry (STPD).

Calibrations

Flow and volume were calibrated with an accurate pump at flows of 50 and 100 ml s^{-1} delivering a volume of 100 ml. The flow from the pump was checked against a precision rotameter and the volume with a spirometer and found to be reproducible within ±0.25%. Flow and volume calibrations were performed before each measurement with the gas composition, temperature and humidification used during the measurements. The Hewlett–Packard capnometer was calibrated before each measurement with gas mixtures with carbon dioxide concentrations between 1 and 7.5% (prepared gravimetrically after actual weight and percentage were determined by gas chromatography) and found to be linear within this range. The mass spectrometer was calibrated daily and before each measurement with certified gases containing 1.31% carbon dioxide, 35.04% oxygen, 63.65% nitrogen and 3.98% carbon dioxide, 49.99% oxygen and 46.03% nitrogen. The reproducibility of the mass spectrometer was investigated by 10 repeated measurements with the same certified gas concentrations. The largest deviation between these repeated measurements was 0.015%.

Procedure

The anaesthetic management was standardized as far as possible. The circuit connections were checked for leaks up to an airway pressure of 15 cm H_2O for children who were breathing spontaneously and up to 25 cm H_2O in those whose lungs were mechanically ventilated. Immediately after intubation of the trachea, nitrous oxide was discontinued and air substituted. No measurements were performed until 30 min after induction of anaesthesia. A 4-min collection period was started, samples and measurements being taken as described above. Immediately after termination of the gas collection, mean fractions of oxygen, carbon dioxide and nitrogen were recorded by the mass spectrometer and expired volumes measured. Anaesthesia was deepened and surgery commenced. The same measurements were repeated approximately 10 min after the start of surgery during a stable state of anaesthesia and surgery in 24 of the 34 children without cardiac disease, and in the four patients with cardiac disease. In the 10 non-cardiac children not studied during operation, the type of surgery did not permit spontaneous breathing.

Statistical analysis

Mean values and standard deviations (SD) were calculated. Linear regressions were performed and standard error of the estimates calculated. Comparisons were carried out with paired two-tailed *t*-tests and probability values < 0.05 were considered to indicate statistical significance.

RESULTS

Mean (SD) values of systolic arterial pressure, heart rate and oxygen saturation before and during surgery are presented in table I. Ventilation was stable during collection periods as indicated by mean (SD) values of tidal volume ($V\text{T}$), rate of ventilation (f), and end-tidal carbon dioxide concentration (E'_{CO_2}) measured at the beginning, middle and end of the 4-min gas collection period, both before and during surgery (table II). Mean (SD) values of $V\text{D}'/V\text{T}$ ratios were 0.18 (0.10) for infants weighing less than 10 kg and 0.15 (0.07) in children weighing more than 10 kg. Corresponding ventilation rates were 45 (14) and 38 (9) b.p.m. The mean concentrations of halothane expressed as age-adapted multiples of MAC were 0.75 (0.9) before and 1.36 (0.32) during surgery in children weighing less than 10 kg and 0.89 (0.17) before and 1.53 (0.31) during surgery in children weighing more than 10 kg. Values of $\dot{V}\text{O}_2$ and $\dot{V}\text{CO}_2$ were similar in the four children with congenital heart disease when compared with the non-cardiac children.

TABLE I. *Mean (SD) values of mean arterial pressure (MAP), heart rate (HR) and oxygen saturation ($S\text{O}_2$) before and during surgery in patients without congenital heart malformations*

	Before surgery (n = 34)	During surgery (n = 24)
MAP (mm Hg)	81.8 (19.9)	87.0 (18.1)
HR (beat min^{-1})	131.8 (26.3)	131.3 (23.3)
$S\text{O}_2$ (%)	97.4 (2.3)	97.4 (2.4)

TABLE II. *Mean (SD) values of tidal volume (V_T), rate of ventilation (f) and end-tidal carbon dioxide concentration (E'_{CO_2}) at the beginning (B), middle (M) and end (E) of the collection period both before and during surgery in patients with a normal cardiopulmonary function* (n = *34 before and* n = *24 during surgery*)

	V_T (ml kg^{-1}) (STPD)			f (b.p.m.)			E'_{CO_2} (%)		
	B	M	E	B	M	E	B	M	E
Before surgery	3.58 (0.79)	3.60 (0.78)	3.50 (0.69)	43.0 (12.0)	43.0 (12.2)	42.0 (12.0)	5.90 (0.81)	5.86 (0.79)	5.84 (0.77)
During surgery	2.78 (0.90)	2.75 (0.81)	2.75 (0.68)	55.6 (15.6)	54.6 (15.0)	54.3 (14.3)	6.26 (0.91)	6.32 (1.0)	6.31 (1.0)

Temperature effects

The coefficient of correlation between body temperature and $\dot{V}O_2$ was 0.14 before and 0 during surgery. The corresponding coefficients for $\dot{V}CO_2$ and body temperature were 0.30 and 0.32, respectively. Similarly, the correlation before surgery was poor both between $\dot{V}O_2$ and the difference between skin and room temperatures (Δ S − R, °C) and between $\dot{V}CO_2$ and Δ S − R with coefficients of correlation of 0.33 and 0, respectively.

Oxygen consumption

There was a linear relationship between $\dot{V}O_2$ (ml min^{-1}) and weight which was described before surgery by the regression equation: $\dot{V}O_2 = 5.0 \times \text{kg} + 19.8$; $r = 0.94$ (fig. 1). The relatively high intercept of 19.8 showed that there was no direct proportionality between $\dot{V}O_2$ and weight for this age group. Consequently, no single mean value could be used for the calculation of $\dot{V}O_2$ and the best estimate of $\dot{V}O_2$ is reached if the regression equation is used as a formula. For children weighing less than 10 kg ($n = 21$), the regression equation between $\dot{V}O_2$ and weight was: $\dot{V}O_2 = 6.8 \times \text{kg} + 8.0$; $r = 0.78$, and for those weighing more ($n = 17$): $\dot{V}O_2 = 4.0 \times \text{kg} + 35.8$; $r = 0.89$.

Oxygen consumption was similar before and during surgery with mean (SD) values of 72.0 (32.0) ml min^{-1} and 69.2 (32.3) ml min^{-1}, respectively. $\dot{V}O_2$ and $\dot{V}A'$ were related linearly to each other and, before surgery, followed the regression equation: $\dot{V}O_2 = 0.07 \times \dot{V}A' + 6.9$; $r = 0.93$ (fig. 2).

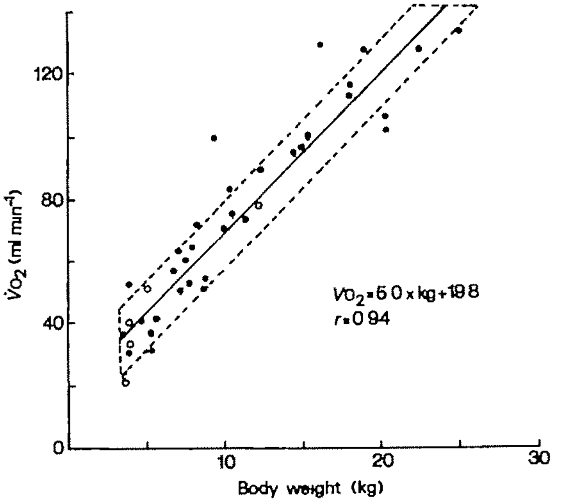

FIG. 1. The relationship between $\dot{V}O_2$ (ml min^{-1}) and body weight (kg). The area between the dashed lines indicates the standard error of the estimate. Open circles denote patients with congenital heart malformations.

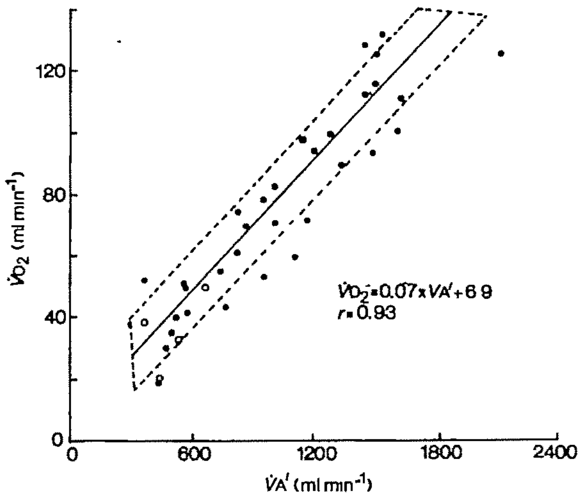

FIG. 2. The relationship between $\dot{V}O_2$ (ml min^{-1}) and alveolar ventilation ($\dot{V}A'$ ml min^{-1}). The area between the dashed lines indicates standard error of the estimate. Open circles denote patients with congenital heart malformation.

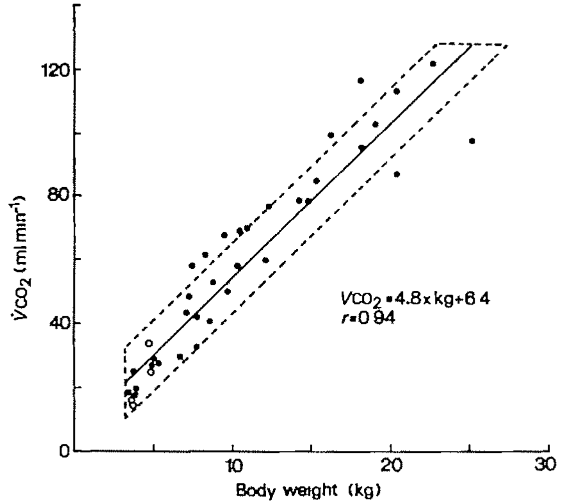

FIG. 3. The relationship between $\dot{V}CO_2$ (ml min^{-1}) and body weight (kg). The area between the dashed lines indicates the standard error of the estimate. Open circles denote patients with congenital heart malformations.

Carbon dioxide elimination

The relationship, before surgery, between $\dot{V}CO_2$ (ml min^{-1}) and weight was described by the regression equation: $\dot{V}CO_2 = 4.8 \times \text{kg} + 6.4$; $r = 0.94$ (fig. 3). Fourteen of the 21 children who weighed less than 10 kg had a $\dot{V}CO_2$ that was below the regression line (fig. 3) and this resulted in a low intercept. If regression analysis of $\dot{V}CO_2$ *v.* weight was used for infants weighing less than 10 kg ($n = 21$), the regression equation for this group was: $\dot{V}CO_2 = 7.2 \times \text{kg} - 8.9$; $r = 0.90$, whereas those weighing more ($n = 17$) followed the regression equation: $\dot{V}CO_2 = 3.7 \times \text{kg} + 25.4$; $r = 0.84$. There were no differences in $\dot{V}CO_2$ before and during surgery.

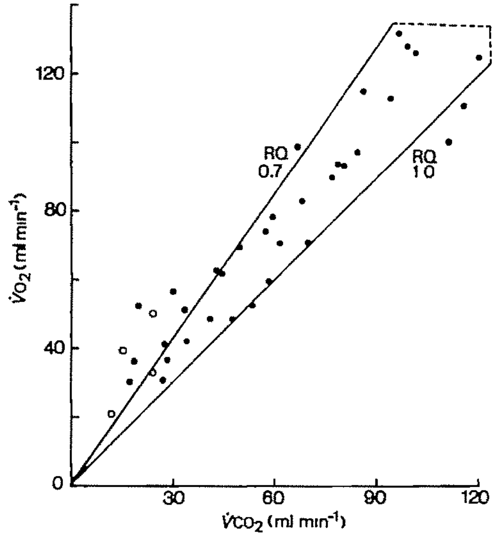

FIG. 4. The relationship between $\dot{V}O_2$ and $\dot{V}CO_2$ for each individual. The area between the lines indicates the range of RQ from 0.7 to 1.0. Note the reduced values for RQ in some of the patients weighing < 10 kg. Open circles indicate patients with congenital heart malformations.

Respiratory quotient

When individual results of $\dot{V}O_2$ and $\dot{V}CO_2$ were related, a discrepancy between the two was found in the youngest patients (fig. 4). This was caused by a relatively lesser $\dot{V}CO_2$ than $\dot{V}O_2$ in infants weighing less than 10 kg, resulting in a reduced RQ. None of the children who weighed more than 10 kg had a RQ less than 0.7.

DISCUSSION

An RQ less than 0.7 justifies a careful scrutiny of measurement techniques. The apparatus was checked for audible leaks and cuffed tracheal tubes were used. However, leaks may occur and pass undetected. Expired gas is mixed homogenously in the distal trachea, shown by the high correlation between $P\text{E}'_{CO_2}$ sampled in the distal trachea, and Pa_{CO_2} in both infants and children [10]. Therefore, leaks of expired gas should not affect RQ measurements. Similarly, a reduction of $\dot{V}\text{E}$ produced by leaks does not affect the RQ, as the same volume is used for the calculation both of $\dot{V}CO_2$ and of $\dot{V}O_2$. Leaks can occur also across the type of non-rebreathing valve used in this study [11]. However, this does not affect the calculation of either $\dot{V}CO_2$ or $\dot{V}O_2$. Methodological errors did not appear to cause the lower than expected RQ in infants weighing less than 10 kg.

This study has confirmed earlier findings [4–6] that $\dot{V}CO_2$ varies in anaesthetized infants with markedly low values in some. This variability in $\dot{V}CO_2$ has been found not only with different measurement techniques, but also during various anaesthetic techniques. When the present data were pooled with previous studies [4, 5] the same variability in $\dot{V}CO_2$ was shown clearly (fig. 5). It may be concluded that this variability is independent of differences in measurement technique or type of anaesthesia and that metabolic causes could be responsible.

Environmental temperature is an important

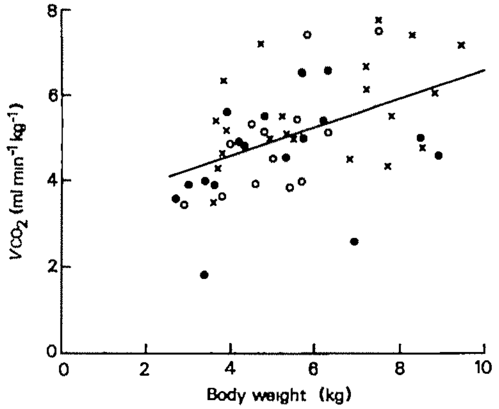

FIG. 5. $\dot{V}\mathrm{CO}_2$ per unit body weight (ml min^{-1} kg^{-1}) related to body weight (kg) for patients weighing less than 10 kg. Closed circles — values from Lindahl, Olsson and Thomson [4]; open circles — from Olsson and Lindahl [5]; crosses — present study. The regression equation for the relationship was: $\dot{V}\mathrm{CO}_2 = 0.33 \times \mathrm{kg} + 3.3$; and the coefficient of correlation 0.44.

factor for metabolic requirements in awake neonates [12, 13], and there is a high correlation for the difference between skin and room temperatures (Δ S − R) and $\dot{V}\mathrm{O}_2$. In contrast to awake infants and children, there was no correlation between Δ S − R and $\dot{V}\mathrm{O}_2$ in these children anaesthetized with halothane. This is in conformity with the findings of Holdcroft [14] who stated that anaesthetic agents reduced heat production and other responses to cold environments. The lack of correlation both between Δ S − R and $\dot{V}\mathrm{CO}_2$ and Δ S − R and $\dot{V}\mathrm{O}_2$ found in this series was seen in all children and showed no age dependency. Temperature-dependent changes in metabolism should have an equal effect on $\dot{V}\mathrm{CO}_2$ and $\dot{V}\mathrm{O}_2$ and leave RQ within normal limits.

$\dot{V}\mathrm{O}_2$ was more predictable than $\dot{V}\mathrm{CO}_2$, and the expected increase in $\dot{V}\mathrm{O}_2$ was found in the youngest patients when expressed on a weight basis. If the regression equation was used as a formula for the estimation of $\dot{V}\mathrm{O}_2$, a 5-kg child consumed 9.0 ml min^{-1} kg^{-1} of oxygen, whereas a 10-kg child had a $\dot{V}\mathrm{O}_2$ of 7.0 ml min^{-1} kg^{-1}. These values are somewhat greater than in non-anaesthetized, healthy, spontaneously breathing neonates [15]. They are greater also than $\dot{V}\mathrm{O}_2$ calculated from the Brody equation ($\dot{V}\mathrm{O}_2 = 10 \times \mathrm{kg}^{3/4}$, where kg$^{3/4}$ represents the lean body mass) [16]. The increase was 35% for infants weighing less than 5 kg and between 20 and 30% for children that weighed more. This suggests that the constant used by Brody should be adjusted for the age of the infant.

In most patients, respiratory quotient varied between 0.7 and 1.0. However, an unexpectedly low RQ was found in some of the youngest patients weighing less than 10 kg. If the age–weight-dependent reduction of $\dot{V}\mathrm{CO}_2$ was caused by generalized metabolic changes, a proportional decrease of $\dot{V}\mathrm{O}_2$ and a normal RQ would have been expected. However, as illustrated in figure 4, this did not occur. The low RQ was caused instead by reduced $\dot{V}\mathrm{CO}_2$. This discrepancy between carbon dixoide output and oxygen consumption may have been caused by hypoventilation and an increased carbon dioxide storage in the body. On the other hand, this was most unlikely, as end-tidal carbon dioxide concentration, tidal volume and rate of ventilation were the same throughout the gas collection period, indicating a ventilatory steady-state during measurements before surgery. Another factor that has to be taken into account is the quantity of glucose infused. In the present study, this was standardized to 3 mg kg^{-1} min^{-1} in order to attain normoglycaemia. It was shown by Nilsson and colleagues [17], that hypoglycaemia did not occur in infants older than a few weeks of age, even if a balanced Ringer acetate solution only was used. It is believed, therefore, that hypoglycaemia was not a cause of the reduced $\dot{V}\mathrm{CO}_2$. Since low RQ values are known to occur in awake neonates [18], the decreased $\dot{V}\mathrm{CO}_2$ seems to result from an age-specific alternate metabolic pathway.

There is one distinct metabolic difference between infants and children: the presence of brown adipose tissue (BAT). This tissue is located mainly in the interscapular region, in the neck and around upper mediastinal blood vessels [19, 20]. The amount of BAT is greater in younger than in older infants. The exact time when it disappears during the first year of life is not known. BAT acts as a thermogenic source in the newborn and young infant and is important for non-shivering heat production in small infants with less well developed muscle tissue. It is rich in blood vessels and has an oxygen consumption higher than normal fat tissue and most other tissues [21]. BAT has an abundant sympathetic innervation [10] and noradrenaline released from nerve endings stimulates lipolysis, which produces carbon dioxide. It has been shown that halothane inhibits lipolysis stimulated by isoproterenol [22]. Sympathetic nerves may be involved with the metabolism of lipids, as denervated rabbit muscle has been shown to accumulate fat [23]. Denervated fat tissue does not participate in fat mobilization, even during starvation and, if nerves to adipose tissue in hibernating mice are damaged, fat mobilization does not occur and the animal dies during a cold stress [24]. Thermogenesis from brown fat is known also to be blocked if local anaesthetic is applied to BAT [25]. These observations suggest that lipolysis and fat mobilization are related to neuronal activity. It may be postulated that halothane inhibited lipolysis in active BAT by "pharmacological denervation" and could lead to the unusually low $\dot{V}CO_2$ seen in this study in small infants. Intermediate lipid metabolites could have accumulated in the body or been excreted through the liver or kidneys, thereby decreasing carbon dioxide production by oxidation, and thus $\dot{V}CO_2$.

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GLYCOPYRRONIUM REQUIREMENTS FOR ANTAGONISM OF THE MUSCARINIC SIDE EFFECTS OF EDROPHONIUM†

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SUMMARY

We have compared, in 60 adult patients, the cardiovascular effects of glycopyrronium 5 µg kg^{-1} and 10 µg kg^{-1} given either simultaneously or 1 min before edrophonium 1 mg kg^{-1}. Significant differences between the four groups were detected ($P < 0.001$). Both groups receiving 10 µg kg^{-1} showed increases in heart rate of up to 30 beat min^{-1} (95% confidence limits 28–32 beat min^{-1}). Use of glycopyrronium 5 µg kg^{-1} provided greater cardiovascular stability and, given 1 min before the edrophonium, was sufficient to minimize early, edrophonium-induced bradycardias. This low dose of glycoprronium provided good control of oropharyngeal secretions.

The reversible cholinesterase inhibitor edrophonium, in doses of 0.5 mg kg^{-1} or greater, has a more rapid onset of effect than neostigmine, together with a lower incidence of muscarinic side effects [1]. Cronnelly, Morris and Miller [2] showed that the atropine requirements of edrophonium are 50% of those of neostigmine.

Previous studies comparing atropine and glycopyrronium as anticholinergics for use with edrophonium, concluded that the former was the agent of choice. However, in these studies glycopyrronium was administered simultaneously with edrophonium [3,4]. Mirakhur and colleagues showed that glycopyrronium has a slower time to peak effect than atropine [5].

The aim of this study was to define a dosage and administration sequence of glycopyrronium with edrophonium which would minimize cardiovascular changes during the antagonism of competitive neuromuscular blockade using this combination.

PATIENTS AND METHODS

Sixty adult patients, ASA I or II, requiring general anaesthesia for elective surgery were studied. Local Ethics Committee approval was obtained, and all patients gave informed consent. No patient was receiving medication affecting neuromuscular function or cardiovascular responses. The patients were allocated randomly to one of four groups using a computer-generated randomization code: *Group A*: glycopyrronium 10 µg kg^{-1} simultaneously with edrophonium 1 mg kg^{-1}. *Group B*: glycopyrronium 5 µg kg^{-1} simultaneously with edrophonium 1 mg kg^{-1}. *Group C*: glycopyrronium 10 µg kg^{-1} 1 min before edrophonium 1 mg kg^{-1}. *Group D*: glycopyrronium 5 µg kg^{-1} 1 min before edrophonium 1 mg kg^{-1}.

The anaesthetic technique was standardized. Following premedication with papaveretum 0.2–0.3 mg kg^{-1} i.m. and hyoscine 4–6 µg kg^{-1} or temazepam 20 mg by mouth, anaesthesia was induced using thiopentone 5 mg kg^{-1}. Intubation and controlled ventilation were facilitated with atracurium 0.5 mg kg^{-1} and anaesthesia maintained with 0.5% halothane and 66% nitrous oxide in oxygen. Opioid supplementation (fentanyl in doses up to 2 µg kg^{-1}) was given if

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clinically indicated. Following completion of surgery, residual neuromuscular blockade was antagonized using one of the edrophonium–glycopyrronium combinations. The glycopyrronium was supplied in coded ampoules containing either 100 µg ml^{-1} or 200 µg ml^{-1}, and administered as 0.5 ml of solution per 10 kg body weight. The investigating anaesthetist was unaware of the dosage regimen to which the patient was allocated, although he was not blinded as to timing of glycopyrronium administration. The facility existed to break the coding for an individual patient.

Cardiovascular data were collected 2 min before administration of glycopyrronium, during the administration, and at 1-min intervals for the 10 min afterwards. During this period anaesthesia and artificial ventilation were maintained with halothane and nitrous oxide in oxygen. Continuous electrocardiographic display (CR5, Cardiac recorders Ltd, using lead CM5) provided information on heart rate and rhythm. Arterial pressure was measured non-invasively, using an automated oscillometric device (Dinamap 845, Critikon Ltd). Edrophonium 1.0 mg kg^{-1} was administered either simultaneously with or at 1 min following glycopyrronium, depending upon the group to which the patient was allocated.

Oropharyngeal secretions were suctioned before administration of the antagonizing mixture, and again before tracheal extubation. The secretions at this stage were graded by the anaesthetist as minimal, moderate or copious.

Statistical analysis of the cardiovascular data was performed using repeated measure analysis of variance. Demographic and other data were analysed for significant differences between the groups using analysis of variance, Fisher's exact test or chi-square test, as appropriate.

RESULTS

The patients were comparable with respect to demographic and control cardiovascular data, taken 2 min before administration of glycopyrronium (table I). No statistically significant differences were detected in the distribution of premedicant drugs or incidence of fentanyl administration between the groups. Comparison of control heart rates between the patients who received temazepam and those who received papaveretum–hyoscine as premedication showed no significant differences.

Analysis of variance showed significant differences in heart rates between the groups ($P < 0.001$). Both groups given glycopyrronium 5 µg kg^{-1} (groups B and D) showed greater stability of heart rate than the groups given 10 µg kg^{-1}. This larger dose of glycopyrronium, administered simultaneously with the edrophonium, produced an increase in heart rate of 30 beat min^{-1} (95% confidence limits 28–32 beat min^{-1}) (fig. 1).

Figure 2 shows the distribution of patients in each group with heart rates less than 60 beat min^{-1}. In the group given glycopyrronium 5 µg kg^{-1} simultaneously with edrophonium, seven patients had heart rates less than 60 beat min^{-1} 1 min after administration of the antagonizing mixture, the slowest individual rate being 42 beat min^{-1}. Administering the dose of glycopyrronium before the edrophonium reduced this incidence; two patients developed rates slower than 60 beat

TABLE I. *Demographic and control cardiovascular data (mean (SD))*

	Group A	Group B	Group C	Group D
n	15	15	15	15
Age (yr)	27.3 (8.2)	29.5 (13.0)	32.5 (11.4)	31.3 (12.0)
Weight (kg)	65.4 (11.4)	66.8 (16.1)	65.4 (13.6)	62.5 (9.4)
Female	11	9	10	9
Premedication				
Temazepam	3	4	7	4
Papaveretum–hyoscine	12	11	8	11
Heart rate (beat min^{-1})	65.3 (11.5)	69.6 (16.2)	74.3 (17.0)	67.3 (10.5)
Systolic arterial pressure (mm Hg)	114 (11.6)	119 (20.7)	118 (12.0)	115 (10.8)

min^{-1} 1 min after the edrophonium, and the slowest rate was 50 beat min^{-1}. The procedure required administration of further increments of glycopyrronium to correct a bradycardia of less than 40 beat min^{-1}, or of less than 60 beat min^{-1} if accompanied by systemic hypotension. This intervention was not required in any of our patients.

Arterial pressure changes, following administration of the antagonizing mixtures, were small in all groups. There was no evidence of any significant differences between the groups, although the power to detect real differences between the groups in a trial of this size is only approximately 33%. However, the largest increase in systolic arterial pressure (seen in the group given glycopyrronium 10 μg kg^{-1} simultaneously with edrophonium) was only 15 mm Hg (95% confidence limits 13–17 mm Hg) greater than the control values.

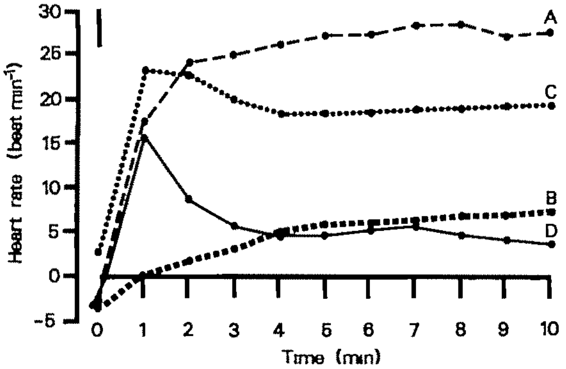

FIG. 1. Change in mean heart rate from control values in each of the four groups; glycopyrronium administered at time zero. Bar indicates the size of the 95% confidence interval for any of the points on the graph. Edrophonium administered at time zero or time 1 min, depending on group (see text).

The only arrhythmias noted were junctional rhythms. The incidence varied between 5 and 7 patients in each group. There were no significant differences between the groups.

There were no significant differences in the amount of oropharyngeal secretions between the groups (fig. 3), with even the lower doses of glycopyrronium providing acceptable control of

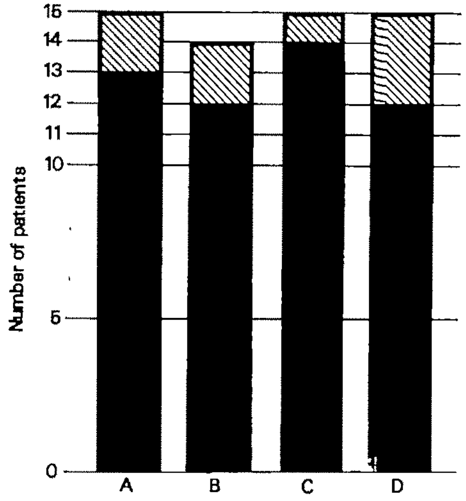

FIG. 3 Anaesthetist's assessment of oropharyngeal secretions. Black columns = minimal secretions; cross-hatched columns = moderate secretions.

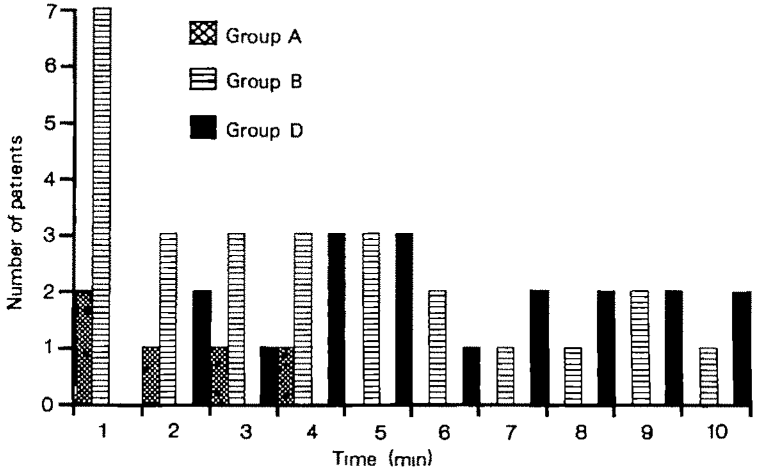

FIG. 2. Patients with heart rates less than 60 beat min^{-1}. No patient in group C had a heart rate of less than 60 beat min^{-1}.

secretions. Analysis of the amount of secretions between the temazepam and papaveretum–hyoscine premedicated patients in each of the groups showed no statistically significant differences.

DISCUSSION

The clinical relevance of haemodynamic changes produced by antagonism of neuromuscular blockade is not yet resolved, although Mostafa and Vucevic [6] demonstrated a significantly greater incidence of ST-segment depression in patients with cardiovascular disease who received atropine in place of glycopyrronium in combination with neostigmine. They postulated that this resulted from greater increases in the rate–pressure product in the patients who were given atropine. Similarly, Tse and colleagues [7] suggested that ST-segment depression detected in the anaesthetic recovery room might be associated with haemodynamic changes, particularly in heart rate, caused by antagonism of neuromuscular blockade. In the light of these studies, it seems logical to select anticholinergic–anticholinesterase combinations which minimize heart rate changes, especially in patients with ischaemic heart disease.

Previous investigators have suggested that simultaneous administration of atropine in a mixture with edrophonium to antagonize neuromuscular blockade provides greater cardiovascular stability than the simultaneous administration of glycopyrronium [3,4]. However, glycopyrronium may have other advantages over atropine; centrally acting anticholinergic drugs may be a factor in postoperative mental impairment. It is well established that anticholinergic drugs can impair memory [8] and a correlation between plasma concentrations of anticholinergic drugs and postoperative delirium has been described previously [9]. In addition, Simpson and colleagues [10] showed that patients who received atropine for premedication and antagonism of neuromuscular block showed postoperative memory impairment 2 days after surgery. Recovery from anaesthesia has been reported to be faster when glycopyrronium is used in place of atropine [11,12]. Based on these findings, the present study was designed to obtain a dosage and administration schedule for glycopyrronium with edrophonium to minimize cardiovascular changes during the antagonism of neuromuscular blockade.

Azar and colleagues [3] showed that glycopyrronium 0.5 mg (approximately 7 $\mu g\,kg^{-1}$) administered simultaneously with edrophonium 0.5 $mg\,kg^{-1}$ provided inadequate protection against early bradycardia. Mirakhur confirmed that the use of low doses (5 $\mu g\,kg^{-1}$) of glycopyrronium administered simultaneously with edrophonium 0.5 $mg\,kg^{-1}$ was often associated with a decrease in heart rate [4]. He showed further that increasing the dose of glycopyrronium to 10 $\mu g\,kg^{-1}$, whilst avoiding the initial bradycardia, was associated with the production of excessive tachycardia [4]. The use of atropine in a dose range of 10–14 $\mu g\,kg^{-1}$ was shown in both studies to provide more stable heart rates. This is in contrast to the previously described superiority of glycopyrronium over atropine as the antagonist of the muscarinic side effects of neostigmine [13].

Our results have confirmed these earlier studies. Additionally, we have demonstrated that the use of a low dose of glycopyrronium 5 $\mu g\,kg^{-1}$ administered before edrophonium minimizes the incidence and severity of the initial bradycardia, whilst avoiding later increases in heart rate. The distribution of premedicant drugs in each of the groups was comparable, and therefore did not introduce a source of bias.

Rupp and colleagues showed that edrophonium should be used in doses of 1.0 $mg\,kg^{-1}$ to provide rapid antagonism of profound competitive neuromuscular blockade [14]. Our results show that this dosage is not associated with an increase in anticholinergic requirement, and provide further confirmation of the weak muscarinic side effects of edrophonium. Further support is shown by the good control of oropharyngeal secretions with the lower doses of glycopyrronium. These findings differ from those of Engbaek and colleagues [15] who suggested that increased doses of atropine were required to accompany higher doses of edrophonium. However, in that study doses of up to 1.5 $mg\,kg^{-1}$ of edrophonium were used in association with very small doses of atropine.

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EXTRADURAL BUPIVACAINE AND METHADONE FOR EXTRACORPOREAL SHOCK-WAVE LITHOTRIPSY†

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Fragmentation of urinary calculi by means of extracorporeal shock wave lithotripsy (ESWL) is accompanied by severe deep pain in the kidney region and superficial pain in the involved skin area. In order to provide adequate pain relief while maintaining stability of the cardiovascular system, which is affected easily during ESWL by immersion in warm water, various general and regional anaesthetic regimens have been described [1–6]. Many patients require analgesic therapy following ESWL, because of abdominal discomfort and colicky pain from the passage of stone fragments.

The successful treatment of ureteric colic in addition to the benefit of supplementation of extradural anaesthesia by extradural opioids has been reported previously [7, 8]. Compared with morphine, extradural methadone was found to be as effective for postoperative analgesia, but with fewer urinary complications [9].

In the present study, the efficacy of low dose extradural bupivacaine analgesia with and without extradural methadone was compared. The quality of post-ESWL analgesia by continuous infusion of extradural methadone with a patient-controlled pump was evaluated also.

SUMMARY

Combined extradural bupivacaine and methadone analgesia was investigated in 144 patients who underwent extracorporeal shock wave lithotripsy (ESWL). Patients were assigned randomly to one of three groups: group I—extradural 0.5% bupivacaine hydrochloride 0.75 mg kg^{-1}; group II—extradural 0.1% methadone hydrochloride 4 mg after the bupivacaine; group III—as group II, plus a continuous extradural infusion of methadone 0.3 mg h^{-1} after operation. In all patients, only partial motor deficit occurred. During ESWL, patients who received extradural bupivacaine and methadone had significantly less pain compared with those who had bupivacaine alone ($P < 0.025$). Extradural anaesthesia and immersion in the warm water bath were accompanied by only mild fluctuations in arterial pressure. After ESWL, significantly more patients with continuous methadone infusion were pain free ($P < 0.05$) and they required less systemic analgesics. The anaesthesia during and after the ESWL procedure may be carried out safely and effectively by the administration of small doses of bupivacaine combined with methadone followed by infusion of the opioid.

PATIENTS AND METHODS

One hundred and forty-four patients undergoing ESWL were studied after informed consent was obtained. The patients received no premedication and were allocated randomly as follows: group I. extradural bupivacaine; group II = extradural bupivacaine and methadone; group III = extradural bupivacaine and methadone anaesthesia and continuous patient-controlled extradural methadone analgesia administered by a syringe pump

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This article is dedicated to the memory of Professor J. T. Davidson, who died during its preparation.

after ESWL. For the purpose of analysis of results, groups II and III were considered to constitute one unit during ESWL.

The extradural needle was placed at the L2–3 or L1–2 space. For extradural anaesthesia a predetermined minimum dose of 0.5% bupivacaine 40 mg (8 ml) or 0.75 mg kg^{-1} (0.15 ml kg^{-1}) was administered through the needle. In the heaviest patients, the maximal dose administered did not exceed 70 mg (14 ml). In groups II and III, 0.1% methadone hydrochloride 4 mg was added shortly after the extradural catheter was introduced. In group III a bolus of extradural methadone 2 mg was added on completion of treatment and the catheter was connected to a portable, battery-operated syringe pump (Model M26, Graseby Medical, England) set to deliver methadone 0.3 mg h^{-1}. These patients were instructed to press a button when in pain, to inject the available drug in boluses of 0.2 mg until analgesia improved. The total dose infused to each patient after surgery did not exceed 5 mg. Midazolam was administered i.v. during ESWL when indicated.

The degree of pain during the ESWL was assessed by the patient, according to the following scale: 1 = no pain; 2 = non-painful sensation of the generated shock waves; 3 = minor pain without need for additional drugs; 4 = pain requiring addition of 1.5% lignocaine 5 ml; 5 = severe pain (change to general anaesthesia).

Twenty-four hours after ESWL, all patients were examined by an independent anaesthetist who was unaware of the anaesthetic procedure, and the pain score was recorded. The need for analgesics was an additional indicator for pain after ESWL and scored as follows: 1 = no need for analgesic drugs; 2 = oral analgesic drugs (dypirone 1 g or pentazocine 30 mg); 3 = i.m. analgesic drugs (pentazocine 60 mg or pethidine 75 mg).

The number of patients in each group, categorized according to analgesic requirement and pain score, was evaluated for statistical significance by the chi-square test. When the phenomena studied occurred with low frequency, Fisher's exact test was used. The differences in the time of onset of pain between the three groups were compared by analysis of variance.

RESULTS

Patient data are given in table I. There were no significant differences between the groups.

TABLE I. *Patient data (mean (SD))*

	Group I	Group II	Group III
No. of patients	45	51	48
Male	33	37	32
Female	12	14	16
Age (yr)	47 (15.7)	50.8 (14.8)	50.7 (11.9)
Weight (kg)	76.1 (14.5)	75 (12.9)	73.9 (10.1)
Height (cm)	168.6 (9.2)	167.7 (8.3)	165.4 (8.6)
ASA score			
I	34	41	43
II	8	6	4
III	3	4	1

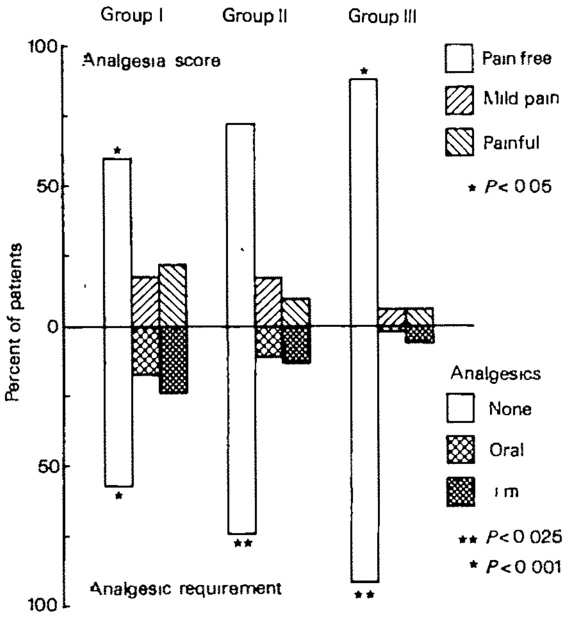

FIG. 1. Post-ESWL analgesia expressed as percentage of patients according to analgesia score and analgesic requirements. Group I = extradural bupivacaine; group II = extradural bupivacaine+methadone; group III = extradural bupivacaine and methadone with continuous methadone by pump infusion.

During ESWL

Extradural anaesthesia with bupivacaine alone (group I) or combined with methadone (group II and III) was associated with mild fluctuations in systolic arterial pressure. A mean maximal reduction of 4.7 (SEM 7)% was observed in group I and of 5.5 (8)% (range −20% to +7.7%) in group II and III. The phase of body immersion in the water bath was accompanied in most of the patients by a small increase in systolic arterial pressure (range −13.6% to +23%). In the course of the procedure hypotension, defined as a systolic arterial pressure less than 90 mm Hg, occurred in seven patients and was corrected by ephedrine 5–10 mg i.v.

Atrial or ventricular premature beats occurred in 10 patients (3.5% of each type) during ESWL, and disappeared when the procedure was discontinued temporarily. Fifty percent of these patients had no previous history of arrhythmia.

Motor deficit was only partial in all patients, enabling unassisted transfer to and from the hydraulic cradle at the start and end of the procedure.

Midazolam 1.5–3 mg was added on 17 occasions (11.9%) when the patient was very tense and after the possibility of insufficient anaesthesia was ruled out. The sedation regulated the patient's breathing; normal ventilation is necessary to help keep the stone within the range of the shock waves.

Extradural anaesthesia provided satisfactory conditions (pain scores 1–3) for ESWL treatment in 98% of the patients in groups II and III and in 86.7% in group I (fig. 1). The patients with pain score 3 (15.6% in group I and 2% in groups II and III combined) had no spontaneous complaints during treatment, but upon questioning at the end of the procedure revealed that they had experienced some minor pain. Severe pain after the original extradural drug administration (scores 4 and 5) occurred in 13.3% of patients in group I and in 2% of groups II and III ($P < 0.001$). All these patients received 1.5% lignocaine 5 ml; in five of them good analgesia was obtained. In two other patients further improvement was achieved by the addition of midazolam. In one patient general anaesthesia had to be administered because of failed extradural blockade. The mean number of shock waves for lithotripsy was 1674 (461), and lasted for a mean period of 35 (18) min.

There was no difference in sensitivity to pain between the two sexes, no difference in distribution of patients according to their body weight between the pain score groups, and no significant change was observed in the pain score as a result of the number of ESWL shock waves administered.

Recovery period

In the first 24 h after ESWL, 60% of patients of group I, 72.6% of group II and 87.5% of group III did not experience pain (scores 1 and 2), and none required systemic analgesics. Those patients in group I who suffered pain reported its onset 5.5 (2.7) h after termination of treatment, while in group II the pain was noted after 7.9 (3.1) h ($P < 0.05$) and in group III after 7.3 (3.3) h. Severe abdominal or colicky pain occurred in 40% of patients in whom anaesthesia consisted of extradural bupivacaine alone. These complaints were noted only in 12.5% of the patients who were treated by continuous infusion of extradural methadone ($P < 0.05$). The total amount of methadone infused did not exceed 5 mg in any patient. In 42.2% of the patients in group I, oral or i.m. analgesics were required, compared with 8.3% in group III ($P < 0.002$). In the patients who received extradural methadone only during ESWL (group II), analgesia seemed to be better after the procedure compared with group I, but the difference not significant statistically. Oral or i.m. analgesic treatment was needed in 25.5% of the patients in group II, significantly more than in those who continued to receive extradural methadone pump analgesia (group III) ($P < 0.025$) (fig. 1).

No serious side effects were encountered. Nausea and vomiting appeared in 31.1%, 43.1% and 37.5% of patients in groups I, II and III, respectively. One-third of those who had nausea vomited also. Two males in group III (4.2%) suffered urinary retention. In one of these, benign hypertrophy of the prostrate was found.

DISCUSSION

The physiological changes resulting from the combination of extradural anaesthesia and body immersion in warm water may be associated with haemodynamic instability [1, 4]. The addition of methadone improved significantly the quality of anaesthesia for ESWL, contributed to a longer duration of the analgesic block, and enabled injection of the local anaesthetic in smaller doses than recommended usually. Hence, haemodynamic stability was obtained and motor weakness minimized during and after the procedure. A similar finding was observed when a mixture of fentanyl and a full dose of bupivacaine was given for extradural blockade [8]. The authors noted that the analgesia obtained was more prolonged, motor blockade was reduced and fewer episodes of acute hypotension occurred than after bupivacaine alone. In the present study, the partial motor blockade may be related to an uneven effect of the low mass of injected anaesthetic drug on the large motor fibres in the spinal cord. The ability of the patients to move themselves almost unassisted to and from the hydraulic cradle was very helpful for the medical staff.

The pain experienced following ESWL results from both tissue injury elicited by the shock waves in the renal area, and elimination of the fragmented stones. The first type of pain is of moderate intensity, insidious and poorly localized, while the second is severe, colicky in nature and is relieved usually only by parenteral opioids. The value of extradural opioids in obstinate cases of ureteric colic pain has been demonstrated already [7]. The present study emphasizes also the efficacy of opioid administration for renal calculi following lithotripsy.

Extradural analgesia combined with injection of a single bolus of methadone, or with continuous methadone infusion, increased both the incidence and duration of the post-ESWL pain relief. The continuous plus "on-demand" patient administration of small doses of extradural opioids is known to provide constant analgesia and effectively fulfils the changing individual requirements with a lower frequency of side effects [10, 11].

The choice of methadone was based on its high lipid solubility, which accounts for a rapid onset of action (approximately 15 min) [9] and rapid elimination from the spinal structures [12]. The use of small volumes minimizes the danger of late respiratory depression as a result of rostral spread. The low rate of urinary retention associated with extradural methadone [9, 13] is an important advantage in patients with urological problems. Usually, extradural opioids produced a higher rate of micturition disturbances, especially when combined with extradural anaesthesia [8, 9]. In the present study, the combination of extradural bupivacaine and methadone administered to urological patients resulted in a low rate of urinary complications. This may be explained by a urodynamic effect after spinal injection of methadone, which has been observed in dogs. It causes an increase in the bladder detrusor tone and, as a result, a low compliant bladder which will accommodate only small volumes of urine [14, 15]; accordingly, an enhancement of the volume-evoked micturition response may have occurred.

Nausea and vomiting, which occurred at a similar frequency in all three groups, might have been related to irritation of the peritoneum and other abdominal viscera by the shock waves, and not to the injected opioid. Anti-emetic drugs alleviated these symptoms.

In conclusion, in patients about to undergo ESWL, the combination of an opioid and reduced amounts of a local anaesthetic drug provides good analgesia during the procedure. In addition, stable haemodynamic conditions are to be expected while the patient is immersed in the warm water. The use of a lipophilic opioid like methadone, with rapid onset of action, may be advantageous. For relief of pain after ESWL, the patient-controlled infusion of extradural methadone may provide analgesia.

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DOES PRETREATMENT WITH CIMETIDINE AND RANITIDINE AFFECT THE DISPOSITION OF BUPIVACAINE?

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SUMMARY

Thirty patients who chose extradural analgesia for elective Caesarean section were pretreated, by random selection, with cimetidine 400 mg, ranitidine 150 mg or no H_2-blocker. Following the administration of 0.5% bupivacaine, no significant difference was found between peak plasma bupivacaine concentrations or area under the plasma bupivacaine concentration–time curve (AUC) in these three groups. This study shows that a single dose of cimetidine or ranitidine does not affect significantly the disposition of bupivacaine in the obstetric patient.

Pretreatment with H_2-receptor antagonists to reduce gastric acidity before anaesthesia is becoming more frequent. In volunteer studies Feely [1, 2] has shown that cimetidine and ranitidine have different effects on the pharmacokinetic profile of lignocaine. They concluded that cimetidine decreased its clearance by inhibiting hepatic enzyme activity and reducing liver blood flow. While reducing liver blood flow, ranitidine had less effect on liver enzyme systems and no effect on the disposition of lignocaine.

Although most investigators agree that the two drugs differ with respect to enzyme inhibition, controversy still exists regarding effects on liver blood flow. In a comprehensive review, Mitchard, Harris and Mullinger [3] suggested that methods of measuring liver blood flow have a significant margin of error. Other studies [4, 5] using the non-metabolized dye, indocyanine green, have failed to show any decrease in liver blood flow following H_2-receptor therapy.

In obstetric practice, treatment with H_2-blockers is associated with the use of bupivacaine for extradural anaesthesia for Caesarean section. In a previous study [6] significantly increased plasma bupivacaine concentrations were found in women receiving ranitidine for antacid therapy. This paper reports an investigation of the effects of pretreatment with H_2-receptor blockers on the uptake, distribution and elimination of bupivacaine given extradurally to patients undergoing elective Caesarean delivery.

PATIENTS AND METHODS

We studied healthy women (36 weeks or more gestation) who selected extradural anaesthesia for elective Caesarean section. Patient and local Medical Research Ethics Committee approval were obtained.

Patients were allocated randomly to three groups to receive cimetidine 400 mg, ranitidine 150 mg or no pretreatment. The H_2-receptor blockers were given by mouth 90–120 min before instituting extradural block. An i.v. infusion of compound sodium lactate solution was commenced and 1.0 litre infused during the establishment of extradural anaesthesia. Hypotension (defined as a reduction in systolic arterial pressure to less than 100 mm Hg) was treated by increasing the rate of infusion and administration of ephedrine 10 mg i.v. An extradural catheter was inserted through the L3–4 space, via a 16-gauge Tuohy needle, leaving approximately 3–4 cm inside the space. Following the uneventful ad-

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ministration of a 2-ml test dose of 0.5% bupivacaine plain, a further 8 ml was given, to produce an initial dose of 50 mg. Incremental doses were given following a 20-min interval (calculated as 1.5 ml per unblocked segment below the level of T6). Further assessment was made 20 min later and an additional increment was required in some patients.

Blood samples were taken from an indwelling catheter in the non-infused arm before local anaesthetic was given extradurally (control sample) and then at 10-min intervals from the first dose of bupivacaine for 90 min. Further maternal samples were obtained at 2, 3, 4 and 5 h. Umbilical vein samples were taken from the cord at delivery of the infant. Each sample was centrifuged and the supernatant plasma stored at −20 °C until required for analysis.

Bupivacaine was analysed by HPLC, using mepivacaine as the internal standard, by a method adapted from that of Park and colleagues [7]. The coefficient of variation of the method of estimation intra-assay was 5.5% at a concentration of 150 ng ml^{-1} and 3.74% at 1 µg ml^{-1}. The interassay variation was 7.5% and 8.5%, respectively.

Arterial pressure and ECG were recorded. The height of sensory blockade was T6 or more in all patients. All results are presented as mean values (SD). Significance of the differences was calculated using the unpaired Student's *t* test and one-way analysis of variance (Anova).

RESULTS

Thirty patients were studied; 10 received ranitidine 150 mg by mouth, 10 cimetidine 400 mg by mouth and 10 no H$_2$-receptor blocker. All groups were comparable for age, weight and parity (table I). Hypotensive episodes occurred in four patients in the ranitidine group, two in the cimetidine group and five in the control group (table II).

Although the total doses of bupivacaine administered to the cimetidine and ranitidine groups were higher than those administered to the control group, the difference was not statistically significant (table III). Mean plasma concentrations obtained at the various sampling times are shown in figure 1.

The maximum concentration (C_{max}) in each group and time of its occurrence (T_{max}) are shown in table IV. The area under the plasma concentration–time curve was calculated for each of the three groups using the trapezoidal rule. Because bupivacaine doses were individualized according to response, varying amounts of local anaesthetic were required. It was necessary, therefore, to normalize AUC in order to compare treatment groups. This adjustment was made using the formula AUC × weight/dose. The results shown in table IV show no statistical difference between the three groups using analysis of variance.

TABLE I. *Patient data (mean (SD))*

	Control (*n* = 10)	Ranitidine (*n* = 10)	Cimetidine (*n* = 10)
Age (yr)	27.5 (4.8)	26.2 (4.9)	28.8 (6.2)
Wt (kg)	69.4 (4.4)	72.6 (9.5)	71.5 (12.0)

The mean terminal half-lives of bupivacaine for the three groups also are shown in table IV. These values were calculated by linear regression using the natural logarithm of the terminal concentration data. None of the differences shown was statistically significant.

There was no difference in Apgar scores of the infants in the three groups. Apgar scores varied between 5 and 9 at 1 min and between 8 and 10 at 5 min. The umbilical vein concentrations and umbilical vein:maternal vein ratios were similar for the three groups (table V). Maternal vein concentrations refer to the sample nearest the time of delivery.

DISCUSSION

Treatment with cimetidine affects the hepatic microsomal enzyme Cytochrome P450, thereby decreasing oxidative metabolism of drugs [8]. This is related to the imidazole ring in its chemical structure. Ranitidine contains a furan ring and has less effect on drug bioavailability [9]. If these agents decrease liver blood flow [10], both would be expected to decrease the clearance of compounds with a high hepatic extraction ratio. However, bupivacaine is a long-acting local anaesthetic, highly protein bound in plasma, and has a low hepatic extraction ratio [11]. It is metabolized in the liver, by the oxidative enzyme system, to pipecolxylidine [12] and only 6% of bupivacaine is excreted unchanged in the urine [13].

Cimetidine and ranitidine are absorbed readily from the gastrointestinal tract, peak blood concentrations occurring within 2 h of oral administration [14]. The initial period of sampling in this

Table II. *Incidence of hypotension*

	Control	Ranitidine	Cimetidine
Episodes of hypotension	5	4	2
No. requiring ephedrine	5	2	2

Table III. *Mean (SD) bupivacaine dose*

	Control	Ranitidine	Cimetidine
Total dose			
mg	99.5 (6.2)	116.0 (21.9)	110.5 (12.0)
mg kg^{-1}	1.44 (0.11)	1.64 (0.46)	1.59 (0.35)
No. requiring three increments	0	6	4

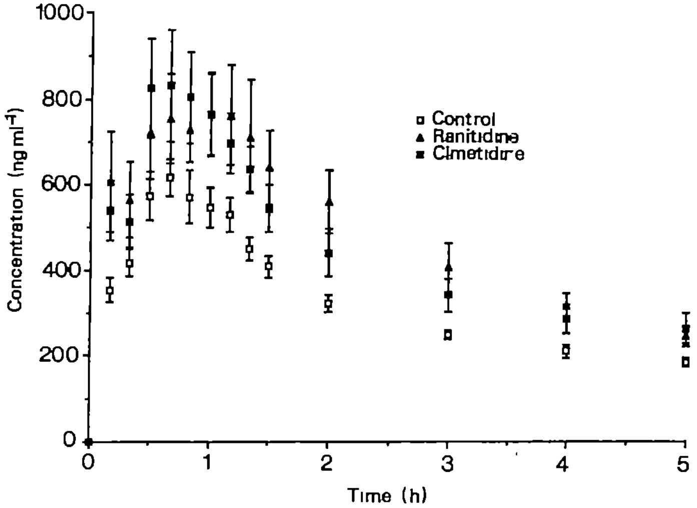

Fig. 1. Mean (SEM) plasma bupivacaine concentrations.

Table IV. *Mean (SD) peak plasma concentration (C_{max}) and time to achieve it (T_{max}), area under the plasma concentration–time curve (normalized using AUC × weight/dose), and terminal half-life ($T_{\frac{1}{2}}^{\beta}$). *Analysis of variance (Anova) $0.1 < P < 0.25$. †Differences between the groups were not statistically significant*

	Control	Ranitidine	Cimetidine
C_{max} (ng ml^{-1})	671 (150)†	914 (397)†	921 (364)†
T_{max} (min)	44 (11)†	47 (24)†	44 (11)†
$T_{\frac{1}{2}}^{\beta}$ (min)	285 (140)	200 (88)	280 (94)
AUC (µg min $litre^{-1}$)	69.20 (11.45)*	88.39 (28.89)*	85.11 (27.65)*

Table V. *Mean (SD) concentrations of drugs in infant blood*

	Control	Ranitidine	Cimetidine
Umbilical vein concn (ng ml^{-1})	186 (130)	221 (92)	229 (103)
UV.MV ratio	0.33 (0.15)	0.33 (0.18)	0.33 (0.19)

study would therefore correspond with therapeutic concentrations of both drugs. In the doses used here, both drugs have been shown to be effective antacids [15, 16].

Blood samples were obtained during intermittent extradural administration of bupivacaine during the initial 40 min so that variations in uptake, distribution and clearance of the local anaesthetic could account for the increased plasma concentrations seen in pretreated patients at these times. Small incremental doses were required at 40 min in six pretreated with ranitidine and four pretreated with cimetidine, compared with none in the control group (table III). This may have influenced the plasma concentrations, but the C_{max} and T_{max} values did not vary between groups. If both cimetidine and ranitidine decrease liver blood flow, a further reduction by autonomic blockade could be a factor in the higher plasma concentrations found in the treated groups. However, as bupivacaine has a slow rate of extraction by the liver, this would seem an unlikely explanation.

In a study which demonstrated no effect from pretreatment with i.m. cimetidine on plasma bupivacaine concentrations [17], there was a 22% increase in unbound bupivacaine when cimetidine was added to bupivacaine-containing maternal plasma. However, as bupivacaine is highly protein bound and has an extraction ratio of 0.3, this effect would enhance removal by the liver. These workers concluded that, as the H_2-blocker reduced hepatic blood flow and increased the free unbound bupivacaine fraction in plasma, these effects on clearance would counter-balance.

The execution of this investigation in a purely clinical setting introduces problems when AUC, clearance and terminal half-life are considered. The initial part of the plasma concentration–time graph was associated with incremental administration of local anaesthetic into the extradural space. As the ultimate aim was to provide a satisfactory sensory blockade for Caesarean delivery, the total dose of bupivacaine given to each patient varied. This slow administration concurred with the view of Thompson and colleagues [18], who considered that the single bolus administration of a predetermined dose of bupivacaine might cause untoward maternal side effects.

The AUC values reported (table IV) are those measured for the first 5 h of sampling. If measured to infinity, AUC is inversely proportional to clearance and therefore comparisons would be made better on the basis of dose administered and body surface area. However, in this case, $AUC_{(0-5\,h)}$ is dependent not only on dose, but also on rate of absorption, apparent volume of distribution and clearance. It is, therefore, more appropriate to adjust the AUC value in terms of dose administered and body weight. The adjustment of AUC values for weight was required because there was a wide range of individual readings, although the mean dose on an mg kg^{-1} basis was similar for the three groups.

Bupivacaine has a terminal half-life of more than 2 h [19], so that a 5-h sampling period was not sufficient to determine accurately the terminal slope of the plasma concentration curve, thereby decreasing the accuracy of the calculated $T_{\frac{1}{2}}^{\beta}$. However, none of these values differed significantly between the treated and control groups. This investigation has shown that single oral doses of cimetidine and ranitidine produced some increase in plasma concentrations of bupivacaine but, as in our preliminary report [20], the increases were not significant.

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Br. J. Anaesth. (1989), **62**, 92–94

MEDIAN NERVE EVOKED POTENTIALS DURING PROPOFOL ANAESTHESIA

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SUMMARY

Median nerve somatosensory evoked potentials (SSEP) were studied in 10 ASA I patients during general anaesthesia with propofol, vecuronium and fentanyl after premedication with diazepam. N14 and N20 latencies, central conduction time (CCT) and corresponding interpeak amplitudes were assessed at induction, after intubation, during steady state, at re-commencement of spontaneous breathing and during early recovery. Data were compared with pre-induction values. Median nerve SSEP were reproducible throughout the procedure and wave forms were suitable for assessment of neurological disorders. Intra-individual changes were considerable for latencies and amplitudes.

During anaesthesia, somatosensory evoked potentials (SSEP) may undergo alterations in latency times and amplitudes which may be interpreted as pathological [1]. The depressant effect of inhalation agents, especially nitrous oxide, exceeds that of the commonly used i.v. anaesthetics [2]. Therefore, i.v. anaesthesia is preferable to use of inhalation agents. This study describes the influence of propofol on median nerve somatosensory evoked potentials.

METHODS AND RESULTS

Ten ASA I patients (mean age 30 (range 17–48) yr) scheduled to undergo minor surgical procedures, were studied. They gave verbal consent to the study, which was approved by the Hospital Ethics Committee.

For signal processing, a two-channel averager was used: The Lifescan EEG Monitor (Neurometrics Inc., San Diego, Ca, U.S.A.). Four electrodes were placed; two on the forehead (Fp_1/Fp_2), one 2 cm posterior to C_3 or C_4 (C_3' or C_4') and one over the spinous process of C_2.

A median nerve was stimulated transcutaneously after assessment of sensory and motor threshold. The stimulus intensity was defined as the current which just caused visible flexion of the fingers. The stimulus rate was 5 Hz: stimulus duration was 16–24 µs, given as square pulse. One sample epoch lasted 100 ms. One run counted 256 samples.

Premedication was with diazepam 10 mg by mouth. Anaesthesia was induced with propofol 2.5 mg kg^{-1}, followed by vecuronium 0.1 mg kg^{-1}. Anaesthesia was maintained with propofol 9 mg kg^{-1} h^{-1}. Patients' lungs were ventilated with 40 % oxygen in air. If needed, supplements of vecuronium were given. For analgesia, bolus doses of fentanyl 1–2 µg kg^{-1} were given, the first after the post-intubation measurement of SSEP. Hypo- or hypercapnia was avoided. Body temperature was maintained within the physiological range.

The N14-latency time (corresponding to arrival of the signal in the medulla oblongata), the N20-latency time (corresponding to cortical potentials generated in the primary sensory cortex) and central conduction time (CCT: the time delay between N14 and N20) were measured. Later cortical deflections tend to disappear during general anaesthesia [3]. The N14-P16 and N20-P23 interpeak amplitudes were measured. Mean interindividual values and intra-individual percentage changes were noted.

The following measurements were compared with pre-induction values: after loss of consciousness; immediately after intubation; 30 min after

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induction (steady state); on regaining spontaneous ventilation; 30 min later during recovery.

Student's *t* test and the Mann–Whitney *U* test were used for statistical analysis.

Pre-induction SSEP were produced in all patients, although excessive muscle artefacts in some patients prolonged the duration of measurements considerably. During anaesthesia a 256-sample run lasted less than 2 min.

In spite of large variations in electrode impedances, median nerve SSEP were observed in all patients during the whole period of measurement. Muscle relaxation and anaesthesia largely decreased signal disturbance. The mean values of impedances of the electrode combinations $C_3'/C_4'-F_p$ and C_z-F_p were 3.0 (1–5) and 4.3 (2–7) kΩ. The mean sensory and motor thresholds were 0.3 (0.1–0.6) and 3.6 (1.3–6.3) mA. The mean stimulus intensity was 6.6 (3.3–11.9) mA.

Deflections later than N14 and N20 almost completely disappeared during propofol anaesthesia. Mean values of N14 and N20 latencies and mean values of the CCT are shown in figure 1. The mean percentage increase in N14 latencies was significant at steady state (3.8 %) and during spontaneous breathing (5.8 %). The mean percentage increases in N20 and CCT were significant only at steady state (8.3 % and 20.2 %, respectively). With the exception of an increase in the N20 amplitude after intubation, mean N14 and other N20 amplitudes did not change significantly.

The amplitudes varied considerably intra- and interindividually. Values for N14 were 4.93 (3.16–6.67) μV before induction and 4.23 (3.39–5.76) μV after intubation. Corresponding values for N20 were 4.09 (2.43–7.52) μV and 5.43 (2.90–8.93) μV. The infusion of propofol lasted 31–121 (mean 66) min and the mean requirement for fentanyl was 4.2 (1.9–7.1) μg kg^{-1} h^{-1}.

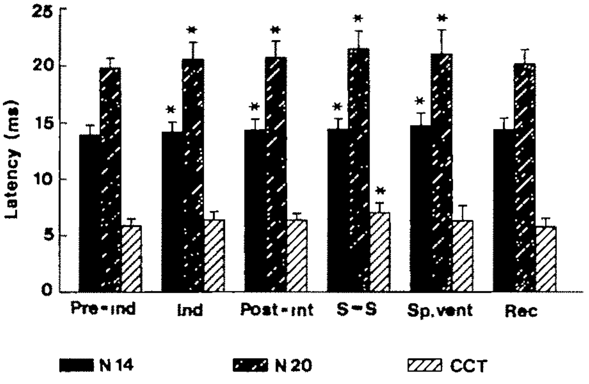

FIG. 1. Latencies (SD bars) of N14, N20 and CCT before induction (Pre-ind), during induction (Ind), immediately after intubation (Post-int), during steady state (S-S), at restart of spontaneous ventilation (Sp. vent) and 30 min after withdrawal of propofol (Rec). * $P < 0.05$ compared with pre-induction values.

Arterial pressure and heart rate changed little during the procedure. End-tidal carbon dioxide concentration varied between 3.7 and 6.4 kPa during the infusion of propofol. During "spontaneous breathing" the end-tidal carbon dioxide concentration was in the range 5.1–8.3 kPa. Body temperatures varied between 37.1 and 35.8 °C.

COMMENT

The interaction between the drugs used in this study on SSEP is not known, as the influence of concomitant use of several drugs for premedication and anaesthesia has not always been considered in the literature [4]. However, diazepam 10 mg probably had no effect on SSEP as Loughnan and colleagues [5] demonstrated that the i.v. administration of diazepam 20 mg had no effect on latency and amplitude of SSEP after 30 and 60 min. Vecuronium is unlikely to influence SSEP and thus the changes occurring on induction and after intubation are attributable only to propofol.

It is difficult to estimate the effect of fentanyl in the doses used. High doses of fentanyl undoubtedly increase latencies and decrease cortical amplitudes, but it has been demonstrated that the N20 latency increases with low doses of fentanyl [4]. Thus an effect of fentanyl cannot be excluded.

It is unlikely that changes in body temperature (ranging from 35.8 to 37.1 °C) influenced the results [2].

Although some patients were subjected to hyperventilation, Schubert and Drummond [3] showed that hypocapnia causes a slight *decrease* in latency times. The N20 amplitude increase after intubation may be influenced by an arousal reaction from the stimulus of intubation. During steady state anaesthesia, amplitudes did not differ significantly from pre-induction values. Studies on inhalation agents demonstrate a considerable decrease in N20 amplitude which is dose dependent [6]. Nevertheless, individual amplitudes varied considerably throughout the procedure. This emphasizes the difficulty of assessing which changes occurring during anaesthesia are pathological. In order to distinguish possible pathological changes from intra-individual or anaesthetic influenced alterations, it is necessary to follow the trend of changes in latencies and amplitudes. It is obvious that bolus doses of drugs should be avoided.

We conclude that the anaesthetic technique described here is appropriate if studies are undertaken on SSEP.

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USE OF CONTINUOUS PROLONGED ADMINISTRATION OF ATRACURIUM IN THE ITU TO A PATIENT WITH MYASTHENIA GRAVIS

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SUMMARY

The case is described of a patient with myasthenia gravis who required prolonged controlled ventilation for respiratory failure. Muscular relaxation was obtained with a continuous infusion of atracurium 5 mg h^{-1} for 45 h. Following cessation of the infusion, paralysis disappeared rapidly.

The use of a neuromuscular blocking drug is avoided frequently in patients with myasthenia gravis because of increased sensitivity to these agents. Occasionally, these patients require admission to an intensive care unit when neuromuscular blockade is necessary to allow controlled ventilation.

A patient with myasthenia gravis is described who required a period of controlled ventilation, neuromuscular blockade for which was obtained using a continuous infusion of atracurium.

CASE REPORT

A 16-yr-old girl with known myasthenia gravis was admitted to hospital complaining of difficulty in swallowing and weak phonation. Myasthenia gravis had been diagnosed approximately 6 months earlier; the weakness affected mainly her bulbar muscles. She had been well controlled with neostigmine and pyridostigmine.

On examination she was pyrexial (38 °C), had coarse crepitations in both lung fields and was expectorating purulent sputum. She was improved transiently by 10 mg of edrophonium and was therefore treated with increasing doses of neostigmine. A course of ampicillin was begun, together with chest physiotherapy. Her weakness did not improve and she began to have difficulty in coughing; progressive respiratory failure necessitated her admission to the Intensive Therapy Unit. On arrival in the ITU she was tachypnoeic (30 b.p.m.), distressed, very weak, and could not cough. Her arterial P_{O_2} was 10.5 kPa with an $F_{I_{O_2}}$ of 0.8 by facemask. Etomidate 16 mg and suxamethonium 50 mg were given, cricoid pressure applied and the trachea was intubated. Controlled ventilation and tracheobronchial toilet were begun, with rapid improvement in oxygenation. Sedation was continued with a loading bolus dose of midazolam followed by a continuous infusion; anticholinesterase therapy was discontinued.

Surface electrodes were placed over the ulnar nerve on one wrist and over the ipsilateral adductor pollicis muscle. These were connected to a Relaxograph (Datex). When recovery from the suxamethonium had reached a constant level in the uncalibrated mode (approx 20 min) the Relaxograph was calibrated. Supramaximal stimulus current was 45 mA, stimulus artefact 2 %, and train-of-four (TOF) ratio 0.84. Bolus doses of atracurium 2 mg were given at 2-min intervals until 100 % neuromuscular blockade resulted (total 8 mg). A dilute solution of atracurium was prepared as 1 mg ml^{-1} in 5 % dextrose and a continuous infusion begun. As neuromuscular function began to return, the infusion rate was adjusted to give a T1 reading of approximately 10–15 % of control on the Relaxograph. This

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infusion rate was 5 mg h^{-1}, and was kept constant throughout.

Sedation and neuromuscular blockade were continued in this way for a period of 45 h. After approximately 20 h, the electrodes were removed, the skin washed and dried, and new electrodes applied over the same sites. This was repeated after approximately 40 h. The Relaxograph was kept on standby mode with periods of stimulation at convenient intervals.

After 45 h, the patient was apyrexial and sputum production was greatly reduced. The decision was made to wean her from controlled ventilation. Pyridostigmine was instilled down the nasogastric tube and the atracurium and midazolam infusions discontinued. Neuromuscular function slowly returned, such that she was able to breathe unaided after 2.5 h. Monitoring was continued, using the Relaxograph, until neuromuscular recovery had reached a steady level. Subsequent recovery was uneventful.

At intervals during the course of the infusion of atracurium and following its cessation, blood samples were taken for measurement of plasma concentrations of atracurium and laudanosine. Atracurium disappeared completely from the plasma within 50 min of discontinuation of the infusion. The amount of laudanosine was also so small that it had been cleared completely within 24 h (table I).

TABLE I. *Height of first twitch compared with control (T1/T0), train-of-four ratio and plasma concentrations of atracurium and laudanosine (assayed using the method of Simmonds [17]) measured at various times during the study*

Time	T1/T0 (%)	Train-of-four ratio	Plasma concn (μg ml^{-1}) Atracurium	Plasma concn (μg ml^{-1}) Laudanosine
After infusion				
0 h	100	0.84	—	—
5 h	15	0.25	0.11	0.10
10 h	12.5	0.20	—	—
20 h	7.5	0.17	—	—
30 h	7.5	0.17	0.21	0.18
40 h	16	0.28	—	—
45 h	15	0.25	0.27	0.29
After infusion discontinued				
5 min	17	0.25	0.16	0.25
10 min	23	0.28	0.09	0.22
20 min	30	0.25	0.09	0.21
50 min	65	0.54	0.00	0.17
2 h	—	—	0.00	0.12
4 h	—	—	0.00	0.03
24 h	—	—	0.00	0.00

DISCUSSION

Myasthenia gravis is an autoimmune neuromuscular disorder affecting the acetylcholine receptors on the postjunctional membrane [1]. Myasthenic patients therefore show an unusual response to neuromuscular blocking drugs [2, 3]. The value of atracurium for intraoperative muscular relaxation in myasthenia gravis is accepted [4–9], and it is probably the agent of choice. The use of atracurium by prolonged continuous infusion in the intensive care management of a myasthenic patient has not been described previously.

In the intensive therapy management of myasthenic patients requiring controlled ventilation, a neuromuscular blocking agent is not often required because the muscles are already weak, and may be made more so by simply reducing the anticholinesterase therapy. It was felt clinically appropriate in this patient, however, to provide relaxation so that aggressive tracheobronchial toilet could be carried out more easily.

The dose requirement of atracurium for use during operation in myasthenia is variable (0.05–0.33 mg kg^{-1}) [4–9]. This is an individual feature of each patient, and appears to be unrelated to anticholinesterase therapy. We found that a dose of atracurium 8 mg (0.22 mg kg^{-1}) was needed for 100 % neuromuscular blockade, which compares closely with the dose requirement for a normal individual [10–12]. Maintenance of blockade was effected with a rate of only 5 mg h^{-1} (0.14 mg kg^{-1} h^{-1}) which, from our own experience, is approximately 20 % of the requirement of a normal adult in a similar situation, and of a normal adult undergoing continuous infusion for surgery [13].

For ease and accuracy of administration, the atracurium was prepared as a dilute solution in 5 % dextrose, spontaneous breakdown being negligible in this diluent [14].

The Relaxograph was found to be satisfactory for the estimation of neuromuscular blockade over this 45-h period. However, we have observed that the response does drift over a prolonged period of time, often not returning to the preblockade control of 100 % on discontinuing administration of the blocking agent. Therefore, it is likely that, after the first few hours, the recorded percent depression was not a true measure of neuromuscular function, although it proved a useful guide and did correlate well with clinical observations. There was some train-of-four fade recorded before administration of the atracurium and it is not possible to ascertain if this resulted from the myasthenia, the suxamethonium or a combination of factors.

Recovery was uneventful, and plasma atracurium concentrations taken during the course of the infusion are compatible with such a low rate of infusion. It is interesting to note that the plasma concentrations which corresponded to approximately 85% neuromuscular blockade in this myasthenic patient were of an order of magnitude similar to those found in other studies at a similar degree of neuromuscular blockade in normal patients [15, 16]. These previous studies, however, examined bolus doses of atracurium, and the recorded measurement of neuromuscular blockade is more likely to have been an absolute value than those we obtained.

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A NEW THERAPEUTIC APPROACH TO ACCIDENTAL INTRA-ARTERIAL INJECTION OF THIOPENTONE

M. VANGERVEN, G. DELRUE, E. BRUGMAN AND P. COSAERT

SUMMARY

After an accidental intra-arterial injection of thiopentone, good therapeutic results were obtained with a selective intra-arterial injection of urokinase during digital subtraction angiography.

A well-known hazard of using thiopentone for induction of general anaesthesia is intra-arterial (i.a.) injection [1]: incidences of 1 in 3440 [2] to 1 in 56000' [3] have been reported. This complication may occur with experienced or inexperienced anaesthetists. The risk is enhanced by factors including obesity, coloured skin, lack of cooperation from the patient, marked thoracic outlet syndrome (abduction and internal rotation of the arm with vanishing pulse pressure), diminished vigilance, and vascular anomalies [3, 4].

Usually, but not always, severe pain radiates along the distribution of the artery immediately after injection. For the first 2 h, the clinical picture varies: the skin may be pale, with subsequent reactionary hyperaemia and possibly cyanosis. Hyperaesthesia, anaesthesia, paresis, paralysis and gangrene with swelling beyond and proximal to the injection site may occur.

Several factors are thought to be responsible for this clinical picture. Arterial spasm caused by local release of noradrenaline was considered very important, but more recent experimental work has shown that this is transient [2–10], unlike the spasm that occurs after traumatic arterial lesions. It was also noted that tissue destruction resulted from thiopentone itself and not the high pH of the solution [8]. Furthermore, intense chemical arteritis was observed after i.a. injection: the endothelium, subendothelium and, in some severe cases, a part of the muscle layer were destroyed [11]. For this reason, thromboplastic factors are released, thrombosis is initiated, and occlusion occurs. This sequence of events is generally accepted [12].

CASE REPORT

A 25-yr-old woman (height 1.6 m, weight 56 kg) was scheduled to undergo laparoscopy. Routine examination revealed slight psychological tension for which she was receiving amitriptyline 10 mg and clomipramine hydrochloride 10 mg three times daily. These were discontinued before operation.

Anaesthesia was induced at 9 a.m. with 2.5% thiopentone 400 mg followed by vecuronium 6 mg and fentanyl 0.1 mg. The injection was made with a 16-gauge i.v. cannula (Venflon) inserted in the lateral aspect of the dorsum of the wrist. No pain was noted at the time of injection. The patient received additional nitrous oxide and enflurane. I.v. fluids were not administered. At the end of the operation, which lasted 20 min, neostigmine 1 mg and atropine 0.2 mg were given. In the afternoon, a slightly painful swelling of the hand was observed with restricted mobility of the wrist. Although the hand was slightly cyanotic, the radial artery pulsated normally. Analgesics and exercises were prescribed.

By the next morning, however, the condition had worsened, both objectively and subjectively. The hand had swollen markedly, the colour had become cyanotic and the mobility of the wrist and fingers was severely restricted. These symptoms could not be accounted for by any other event during the surgical procedure, such as venous obstruction caused by improper positioning or the use of the tourniquet. In addition to symptomatic

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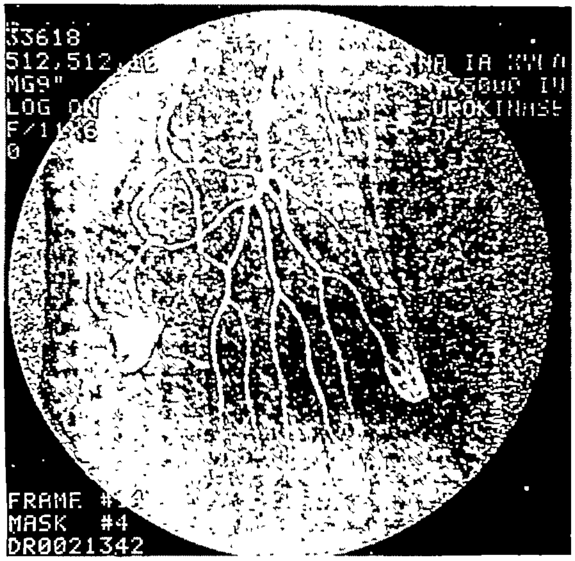

FIG. 1. Intra-arterial digital substraction angiogram of the right hand 22 h after i.a. injection of thiopentone.

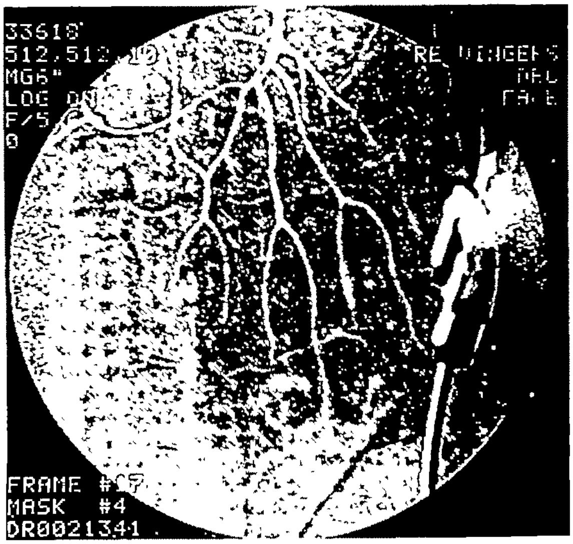

FIG. 2 Intra-arterial digital substraction angiogram of the right hand 15 min after the selective i.a. injection of urokinase 75000 iu.

therapy, xanthinol nicotinate 3000 mg/24 h i.v. was started. A stellate ganglion block with 0.5% bupivacaine 10 ml was performed successfully. Two hours later a digital subtraction angiograph of the right arm was performed via the right common femoral artery (22 h after the initial event). Selective injection of a non-ionic contrast product, iohexol (Omnipaque) 180 mg ml^{-1}, showed normal filling of the radial artery and the ulnar artery. There was normal filling of the superficial and deep palmar arches. The digital arteries filled only to the proximal interphalangeal joint. There was no evidence of emboli (fig. 1). Ten millilitre of 2% lignocaine (Xylocaine) was injected i.a. and a repeated angiogram showed no change. Twenty minutes later, Urokinase 75000 iu was injected. A third angiogram 15 min after this injection showed good filling of the digital arteries and a clear parenchymal blush (fig. 2).

To obtain maximal vasodilatation, another stellate ganglion block was performed the next day (10 a.m.). The clinical course was favourable subsequently, and the patient was discharged 5 days later. Slight residual swelling disappeared in 2 weeks, and there were no further problems.

DISCUSSION

No local anaesthetic was used at the insertion of the i.v. cannula, which was atraumatic. The puncture had been made after palpation, but whether or not the tourniquet had been inflated to more than the systolic arterial pressure could not be ascertained. This would, of course, increase the risk of i.a. insertion of the cannula.

It was long thought that sufficiently diluted solutions (2.5%) did not cause irreversible damage [11–13], but several authors have recently reported gangrenous lesions after i.a. injection of 2.5% thiopentone [14, 15]. Until now, therapy has concentrated mainly on dilution of the injected thiopentone, prevention of and therapy for arterial spasm, prophylaxis of thrombosis, thrombectomy and general measures to sustain good blood flow. Nevertheless, the prognosis was often poor.

The authors were encouraged to use a thrombolytic agent in this patient as it is widely accepted that the pathogenesis is progressive thrombosis resulting from the endothelial lesion [12]. Urokinase was preferred rather than other thrombolytic agents because of experience with this product in our hospital, and because few side-effects are to be expected [16–18]. No disturbances in activated partial thromboplastin time, prothrombin time, fibrin degradation products, or platelet count were found 2 h after the injection of urokinase. Although the results obtained in this patient are encouraging, further study is required to determine the role of urokinase in the management of accidental intra-arterial injection of thiopentone.

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NEUROGENIC PULMONARY OEDEMA PRECIPITATED BY INDUCTION OF ANAESTHESIA

N. BRAUDE AND T. LUDGROVE

SUMMARY

Neurogenic pulmonary oedema is a recognized complication of central nervous system injury. A case is presented where this condition was precipitated by induction of anaesthesia in a child with spina bifida, hydrocephalus and a malfunctioning ventriculo–peritoneal shunt.

Neurogenic pulmonary oedema (NPO) develops in a small proportion of patients suffering a central nervous system insult. We report a case of neurogenic pulmonary oedema precipitated by induction of anaesthesia.

CASE REPORT

A 12-yr-old boy (weight 53 kg) with spina bifida and hydrocephalus (previously controlled with a ventriculo–peritoneal shunt) was admitted to hospital with a 6-day history of headache and nausea. Previous anaesthetic history consisted of closure of myelomeningocoele as a neonate, later insertion of a ventriculo–peritoneal shunt and subsequent revision for blockage. All these procedures were accomplished without incident.

On examination there were no features of increased intracranial pressure (ICP) or evidence of alteration of level of consciousness. Examination of the ventilatory and cardiovascular systems was normal, as was the preoperative chest x-ray. Skull x-ray revealed a disconnected ventricular shunt. Whilst preparations for surgery were completed, 4% dextrose 140 ml in 0.18% saline was infused i.v. over a 3-h period.

No premedication was given. Anaesthesia was induced with thiopentone 225 mg and fentanyl 50 µg; paralysis was achieved with suxamethonium 75 mg and the trachea intubated with a size 7.0 uncuffed oral tracheal tube. Neuromuscular blockade was maintained with atracurium 25 mg and the patient's lungs were hyperventilated by hand through a Magill circuit (fresh gas flow rate 9 litre min^{-1}) while the head was shaved; the latter involved rotating the head to the left. Anaesthesia was maintained with 0.5% halothane and 67% nitrous oxide in oxygen. Within 5 min, difficulty was experienced in ventilating the lungs because of an increasing leak around the tracheal tube; the patient was noted to be cyanosed centrally. The tracheal tube was changed to a cuffed version but, despite improved ventilation and 100% oxygen, the patient remained cyanosed. Auscultation of the chest was unremarkable and there were no cutaneous manifestations of anaphylaxis. Frothy blood-stained fluid was now obtained on tracheal suction. The patient was transferred from the anaesthetic room to the operating theatre where monitoring revealed a haemoglobin oxygen saturation of 65% ($F\text{I}_{\text{O}_2}$ 1.0), a heart rate of 180 beat min^{-1} (sinus tachycardia) and arterial pressure of 160/120 mm Hg; approximately 15 min had elapsed since induction of anaesthesia. Frusemide 80 mg and a further fentanyl 150 µg were administered i.v. and the patient was prepared for emergency revision of the ventriculo–peritoneal shunt. Controlled ventilation was continued with a Penlon 200 ventilator, using oxygen 9 litre min^{-1} via a Bain Circuit.

At operation, disconnection of the shunt proximal to the valve was confirmed and the intra-

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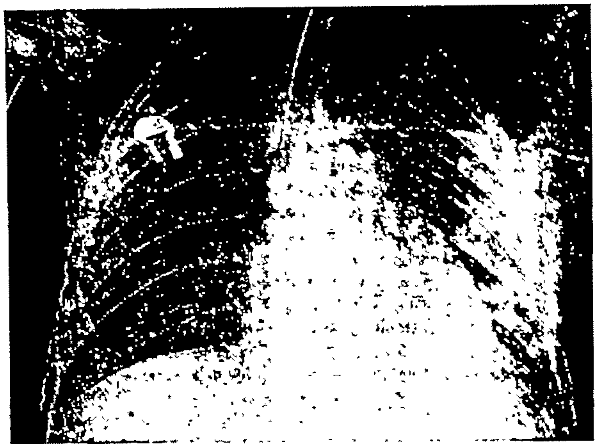

FIG. 1. Antero-posterior chest radiograph taken at the end of shunt revision. Note the diffuse lung-field shadowing and air bronchograms, the apparently normal heart size and the ventriculo-peritoneal shunt.

ventricular pressure was found to be increased significantly (more than 300 mm H_2O (22.8 mm Hg). The shunt was revised and free flow confirmed. A chest x-ray taken immediately after operation showed bilateral diffuse shadowing of the lung fields (consistent with pulmonary oedema) and the heart size within normal limits (fig. 1); arterial Po_2 was 4.9 kPa. The patient was transferred to the Intensive Therapy Unit.

Full ventilatory support with sedation, neuromuscular blockade and positive end expiratory pressure (PEEP) was continued for a further 12 h. During this period there was a marked improvement in oxygenation and minute volume requirements. Chest radiography at this point demonstrated virtually total resolution of abnormal changes. The trachea was extubated 18 h after the onset of pulmonary oedema, but the patient required naloxone 3 h later for opioid-induced respiratory depression. The remainder of his course was uncomplicated.

DISCUSSION

Neurogenic pulmonary oedema (NPO) has not been described previously in association with induction of anaesthesia, although it has been reported widely as a sequel to neurosurgery and anaesthesia. Typically, it develops some hours after a central nervous system insult [1], but rapidly fulminating cases have been described in association with massive neurological injury [2].

An associated Arnold–Chiari malformation is present in virtually all children with spina bifida [3] and in early life respiratory depression and sleep apnoea are well recognized; this is thought to be in part secondary to compression of respiratory centres in the medulla [4]. Experimental evidence suggests that central nervous system trigger-zones for the development of NPO are located in the medulla [5] and that massive trigger-zone stimulation results in a profound sympathetic discharge, an increase in pulmonary microvascular pressure and consequent damage to endothelial integrity [6]; lesser degrees of stimulation may alter endothelial permeability directly, without a preceding increase in hydrostatic pressure [1]. Hence, it seems likely that the pressor response of intubation, intermittent positive pressure ventilation through a Magill circuit and the early introduction of halothane produced a critical increase in intracranial pressure (ICP) which, together with the presence of an Arnold–Chiari malformation, precipitated a fulminant form of NPO; the position of the head during shaving may have compromised intracranial venous drainage and thereby further increased ICP.

The reason for the relative rarity of NPO in anaesthetized patients with pre-existing intracranial hypertension remains uncertain. A hypothesis based solely on anatomical predisposition is not supported by experience with this patient, as a similar anaesthetic sequence for a blocked shunt had been used without complication 4 yr earlier.

Pulse oximetry used throughout induction of anaesthesia would undoubtedly have resulted in earlier recognition of hypoxia and thus NPO. Prevention of NPO in this patient may have been possible by attenuating the intubation-related increase in ICP by pretreatment with i.v. lignocaine [7], the use of a non-depolarizing neuromuscular blocking drug [8] and ventilation with a more efficient circuit.

There is wide consensus that management of established NPO should be aimed at reducing ICP and supporting ventilation if necessary [1, 6, 9]. Alpha-blocking agents and vasodilators have been proposed as a means of attenuating the sympathetic pressor response [9] but, as mentioned above, the pressor response does not appear to be a prerequisite for the development of lung permeability changes; in any event these agents would exacerbate intracranial hypertension and further reduce cerebral perfusion pressure.

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FATAL HAEMOPATHOLOGICAL CONSEQUENCES OF GENERAL ANAESTHESIA

P. J. WRIGHT, J. R. SHORTLAND, J. D. STEVENS, M. A. PARSONS AND J. WATKINS

SUMMARY

A previously healthy 63-yr-old female died following an anaphylactoid response to anaesthesia with thiopentone and suxamethonium. Postmortem findings strongly suggested that disseminated intravascular coagulation played a significant role in her death. The local mechanism behind the reaction is unknown, but the formation of thiopentone–suxamethonium colloid aggregates during induction, may have lead to "aggregate anaphylaxis".

The original classification of adverse drug reactions into Type A (exaggerated but otherwise normal pharmacological response), and Type B (unusual pharmacological response) [1] is irrelevant to the rapid onset reactions encountered during induction of anaesthesia. The most hazardous situation encountered by the anaesthetist is the immediate hypersensitivity response. These reactions, which unfortunately seem to be increasing in number annually [2,3], are largely unpredictable. The reaction, which is manifest anaphylaxis, is described best as anaphylactoid pending investigation of the aetiology, and corresponds to Type B reactions of the older classification.

Anaphylactoid reactions to i.v. anaesthetic agents range from skin rashes to an overpowering systemic response causing bronchospasm, hypotension and cardiac arrest. Several mechanisms may operate in these anaphylactoid reactions which lead ultimately to an adverse clinical response [4,5]. The importance of obtaining a history of allergy from the patient or relatives during the preoperative assessment has been emphasized by others [6,7]. However, reviews of anaphylactoid reactions to thiopentone suggest that 80% occur without prior exposure, and do not involve antibodies of any type [2].

A moderately obese and anxious 63-yr-old female presented for ulnar nerve release under general anaesthesia. Her past history revealed two previous general anaesthetics, 16 and 3 yr before this event. After premedication with papaveretum 15 mg and prochlorperazine 12.5 mg, anaesthesia was induced with thiopentone 175 mg and suxamethonium 75 mg i.v. to facilitate tracheal intubation. A white precipitate formed in the tubing of the self-sealing infusion set when the suxamethonium was injected. There was a shallow cough, followed by bradycardia, severe bronchospasm and hypotension. Despite tracheal intubation and ventilation of the lungs with 100% oxygen, cyanosis progressed and cardiac arrest occurred. The patient was treated with i.v. atropine, calcium chloride, chlorpheniramine and adrenaline. Cardiopulmonary resuscitation was successful initially, but the patient died 7 h later without regaining consciousness.

At postmortem the most notable macroscopic features were seen in the lungs which displayed oedema, and haemorrhagic foci on both the external and cut surface (fig. 1). There was a moderate degree of generalized non-occlusive atheroma, and the liver appeared slightly greasy on cut surface. Histology of the lungs revealed extensive haemorrhage and proteinaceous material within the alveoli, with intra-alveolar fibrin in some areas. There was recent thrombus formation in small pulmonary arteries (3 mm) (fig. 2), and

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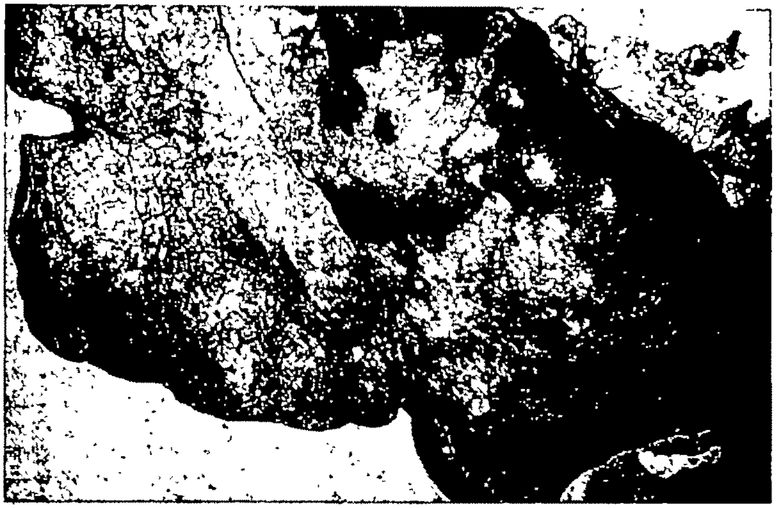

FIG. 1. Haemorrhagic foci on both the external and cut surface were the prominent features in the lungs.

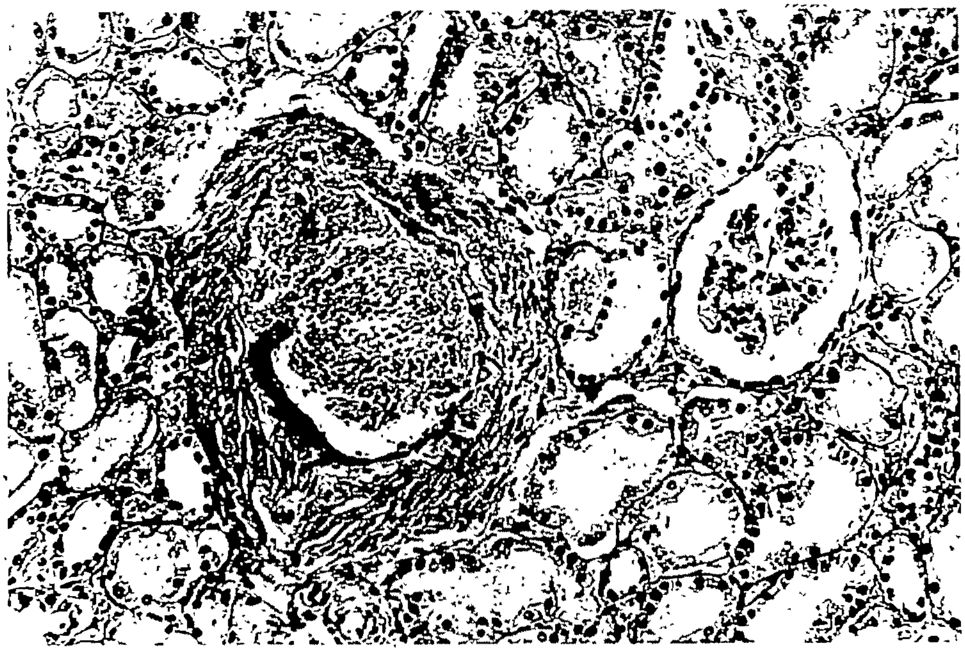

FIG 2. A recent thrombus is present in a small pulmonary artery. (H&E × 20.)

evidence of fibrin deposition in capillaries and precapillary arterioles. Intravascular thrombosis was identified also in renal (fig. 3) and cerebral vessels.

DISCUSSION

Because of the polypharmacy involved in modern anaesthesia, many reactions are probably synergistic and involve several of the drugs administered; the combination thiopentone–suxamethonium is the most hazardous and the most frequently used [8]. Few reactions are drug-specific (immune). Excluding idiosyncrasy and concomitant disease, the majority of non-immune reactions are, unfortunately, likely to reflect anaesthetic technique. All other reactions are

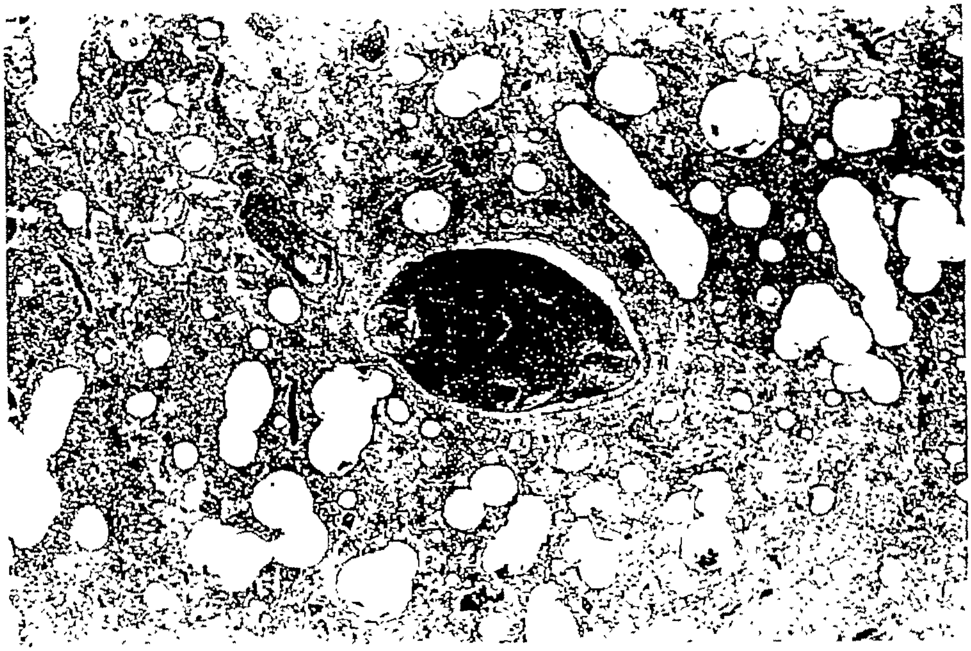

FIG. 3. Intravascular thrombosis is present in renal arteries. (H&E × 220.)

indistinguishable clinically from true anaphylaxis [4,5].

Two of the most hazardous mechanisms involve the rapid administration of several drugs through a cannula sited in a small vein. These involve synergistic histamine effects, usually alarming but managed readily, and aggregate anaphylaxis [9]. The latter is likely to occur when drugs with very different physicochemical properties are allowed to mix in the indwelling cannula (deadspace usually 0.1 ml). Although the most common and transient phenomenon is a harmless localized thrombophlebitis, on occasions precipitates form, which may also involve plasma proteins, and assume a colloid, soluble nature [4,10]. These colloids are sequestrated actively by the pulmonary microvasculature, leading to occlusion. Activation of the biological systems within the lungs and elsewhere results in blood polymorph and platelet aggregation [11], manifest in various haematological sequelae [12], notably of the shock-lung variety [13–15]. The histological features in the present patient clearly show disseminated deposition of fibrin, and alveolar involvement consistent with such a mechanism. However, the precise local mechanism within the lungs is at present unknown.

It seems that the risk of reactions might be much reduced by the avoidance of the small vein/cannula technique. Instead, the drugs should be injected into a large vein, where the larger volume of blood and its movement would preclude the formation of colloid aggregates. If the small vein technique is to be followed, then at least a flush with saline should take place between drugs and, ideally, there should be an interval of 2–3 min between the administration of different drugs.

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ACUTE GASTRIC DILATATION IN AN INCARCERATED HIATUS HERNIA

C. S. HOPKINS AND S. LEITH

SUMMARY

A case is reported of an unusual complication in which acute gastric dilatation occurred in an incarcerated hiatus hernia, resulting in left ventricular failure in the postoperative period. Failure to recognize this gave rise to concern when the patient re-presented for further surgery.

The pathophysiology of acute intra-abdominal gastric dilatation following general anaesthesia has been reviewed previously [1]. This condition may be complicated by hypovolaemic shock, electrolyte imbalance and aspiration pneumonia [2]. Complications arising from acute dilatation in an incarcerated hiatus hernia have not been reported previously in the anaesthetic literature.

CASE REPORT

A 76-yr-old female was admitted to hospital with a fractured neck of femur. She was unable to give a history, but had been suffering from senile dementia for many years. She was scheduled for dynamic hip screw fixation under general anaesthesia.

Physical examination revealed a frail physique with dorsal scoliosis and pectus recurvatum. Cardiovascular examination revealed a regular heart rate (70 beat min^{-1}), normal jugular venous pressure, arterial pressure 140/80 mm Hg, no sacral or peripheral oedema, cardiac apex not palpable and normal heart sounds with no added sounds. Haematological and biochemical indices were within normal limits for the patient's age. The electrocardiogram showed sinus rhythm with no evidence of ischaemia, previous myocardial infarction or conduction abnormality. The chest radiograph was not reported formally before operation (fig. 1).

No premedication was prescribed. The patient's lungs were pre-oxygenated with 100% oxygen before induction of anaesthesia with thiopentone 125 mg i.v. Intubation of the trachea was facilitated by use of suxamethonium 75 mg i.v. Anaesthesia was maintained with oxygen, nitrous oxide and enflurane. Neuromuscular blockade was maintained with atracurium 30 mg and analgesia supplemented with morphine 4 mg.

ECG, heart rate and arterial pressure were monitored throughout and remained within 10% of preinduction values. Surgery lasted 70 min. A total of 400 ml of whole blood was infused to replace measured blood loss. At the end of the procedure residual neuromuscular blockade was antagonized with neostigmine 2.5 mg and glycopyrrolate 0.5 mg. Recovery was uneventful and the patient was transferred to the ward 1 h after operation. Thirty-six hour later she became increasingly dyspnoeic, heart rate was 130 beat min^{-1}, arterial pressure 170/90 mm Hg with an increased jugular venous pressure. Auscultation revealed poor air entry bilaterally, with expiratory wheeze and fine rales, and an audible third heart sound. ECG showed sinus tachycardia with no evidence of recent ischaemic change. Arterial blood-gas analysis showed pH 7.41, Pa_{O_2} 14 kPa (FI_{O_2} 0.6), Pa_{CO_2} 4.2 kPa, standard bicarbonate 21 mmol litre^{-1} and base deficit -4 mmol litre^{-1}.

Portable chest x-rays were said to be technically very poor, but no pneumothorax was seen (figs 2, 3).

Treatment comprised frusemide 80 mg i.v.,

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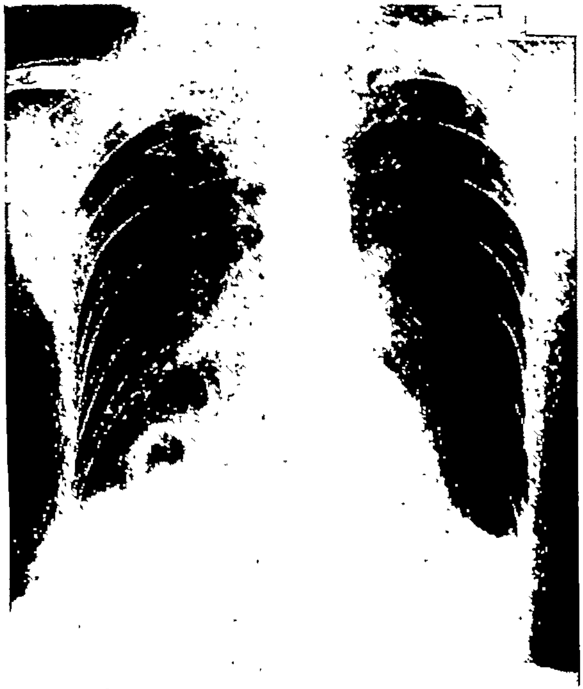

FIG. 1. Erect x-ray of the chest on admission to hospital. Gas shadows with a fluid level are clearly visible around the right heart border.

aminophylline 250 i.v. over 15 min, hydrocortisone 200 mg i.v. and nebulized salbutamol, in addition to diamorphine 5 mg i.v. The patient improved gradually and required no further treatment overnight. The following day it was noticed that the hip had become displaced and an anaesthetic assessment was requested regarding further surgery in the light of presumed recent left ventricular failure.

On examination there were no new physical findings. Heart rate was 80 beat min^{-1}, arterial pressure 130/70 mm Hg, with no jugular venous distension. Auscultation revealed normal heart sounds, but active bowel sounds were heard over the left chest. The interpretation of events based on a review of all x-rays was that, on admission, gastric and bowel gas was seen clearly around the cardiac outline (fig. 1)—evidence of an incarcerated hiatus hernia. The x-rays during the acute deterioration showed marked gaseous distension occupying most of the mediastinum with associated pulmonary congestion (figs 2, 3). On the following day there was less gaseous distension and the lung fields were clear.

At this stage the patient resisted all attempts to pass a nasogastric tube, but it was felt that there was no contraindication to a further operative procedure under general anaesthesia. A rapid sequence i.v. induction with cricoid pressure was performed after pre-oxygenation, using etomidate 10 mg i.v. and suxamethonium 50 mg i.v. A nasogastric tube was passed subsequently without difficulty. Anaesthesia was maintained with nitrous oxide in oxygen supplemented by enflurane. Vecuronium 5 mg was given to facilitate IPPV and morphine 3 mg given during operation. Residual neuromuscular blockade was antagonized by neostigmine 2.5 mg with glycopyrrolate 0.5 mg after 60 min. Postoperative x-ray taken in the recovery area showed there was still some bowel gas present in the mediastinum, but that the stomach remained decompressed (fig. 4). The nasogastric tube remained in place and there were no further problems in the early postoperative period. In spite of intensive chest physiotherapy and antibiotics, the patient died 6 weeks later with bronchopneumonia.

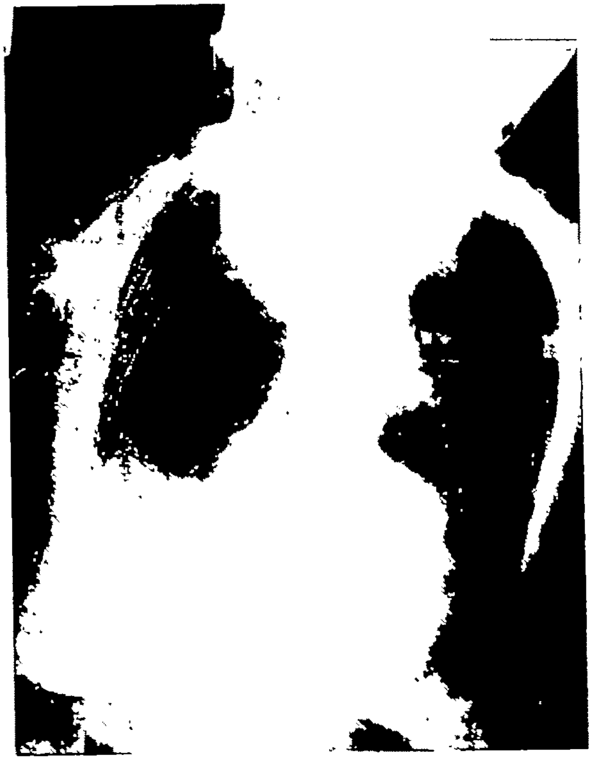

FIG. 2. A rotated x-ray of the chest taken at the time of maximum respiratory distress. Gross dilatation of the stomach is evident, with pulmonary vascular congestion

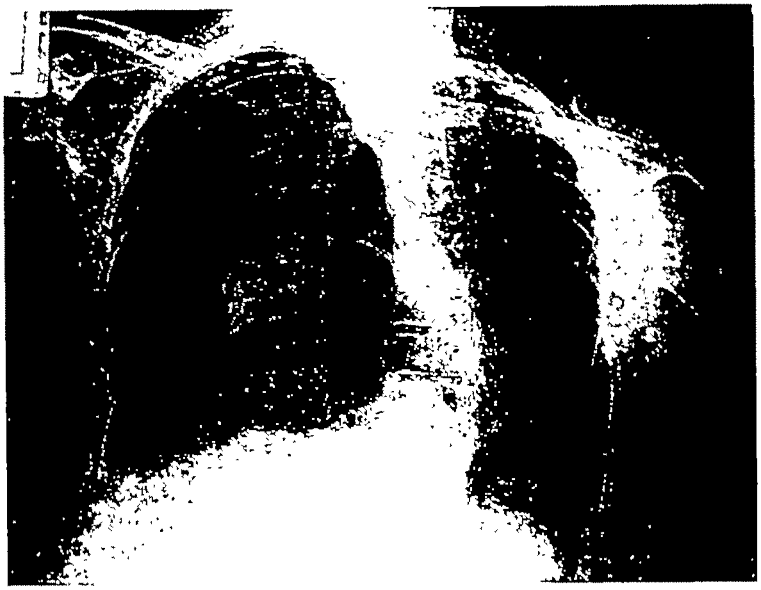

FIG. 3. X-ray of the chest taken 4 h after treatment of respiratory distress. The degree of gastric dilatation is less and the lung fields have cleared.

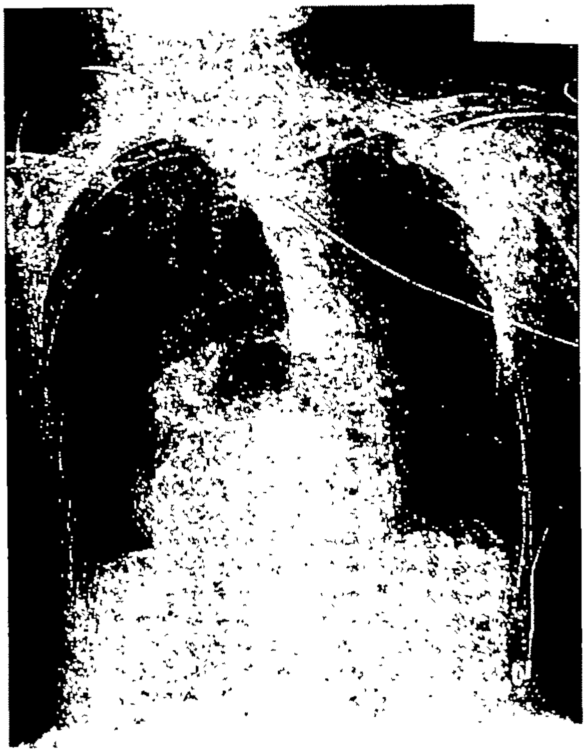

FIG. 4. X-ray of the chest taken in recovery after the second operation. A nasogastric tube is in place and the stomach is decompressed. Some bowel gas is still present.

DISCUSSION

The pathophysiology of acute gastric dilatation is well known and has been reviewed [1]. We have been unable to find any reference to this problem occurring in an incarcerated hiatus hernia in the postoperative period. In its usual position, rapid distension of the stomach leads to mucosal congestion and bleeding, with considerable third space fluid sequestration. In a Type II or paraoesophageal hiatus hernia, there is a defect in the phreno–oesophageal membrane, permitting a peritoneal sac to enter the thoracic cavity. If acute dilatation occurs in this case, expansion of the stomach would be limited by the borders of the mediastinum. It could affect cardiac output by reducing ventricular filling by direct compression or by interfering with systemic or pulmonary venous return. A visceral–cardiac reflex has been suggested as the cause of haemodynamic alterations in intra-abdominal dilatation [3].

In our patient, the response to diuretic, morphine and aminophylline therapy suggests that there was an increase in left ventricular filling pressure. A more rapid response may have been achieved if the x-ray appearances had been interpreted correctly and a nasogastric tube passed.

The role of nitrous oxide in this case is debatable. During the first operation there may have been diffusion of nitrous oxide into the incarcerated stomach which already contained a gas bubble as seen on the preoperative x-ray. This could have initiated a sequence of distension, mucosal ischaemia and increased secretion which continued into the postoperative period. The majority of cases of intra-abdominal gastric dilatation are reported to occur in the first few days following surgery [4].

The lessons to be learned from this patient are that a gas bubble in the mediastinum indicates a potential for intrathoracic visceral dilatation in the postoperative period, requiring that a nasogastric tube should be passed and aspirated continuously; and that apparent acute left ventricular failure in patients with an incarcerated hiatus hernia also indicates that a nasogastric tube should be passed as part of the management of the patient.

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CORRESPONDENCE

HYPOTENSIVE AGENTS: AN ANIMAL MODEL

Sir,—I query the choice of the greyhound by Sury and colleagues [1] as an animal model for the cardiovascular actions of hypotensive agents. The authors cite the greyhound's compensatory mechanisms and their similarity to healthy young adults. There are certainly several reasons why the greyhound is an attractive experimental animal, including species homogeneity, adequate size, lack of body fat, large thorax and conduit blood vessels for instrumentation.

However, the characteristics of the greyhound cardiovascular system compared with those of the mongrel are well documented, and include higher mean arterial pressure and cardiac index with a lower calculated peripheral vascular resistance in the unanaesthetized animal, differences in haemodynamic responses to i.v. anaesthetic induction, lower plasma renin concentrations in anaesthetized and non-anaesthetized animals, together with multiple differences in central and regional pulsatile haemodynamics [2]. The ability to compensate for perturbations in arterial pressure in the intact greyhound is not significantly different from that of mongrel controls of comparable age and weight. Differences in regional baroreceptor haemodynamic control are confined to skeletal muscle [3]. In many ways, as an experimental animal model, the greyhound resembles the early phase of benign human essential hypertension.

R. J. Bagshaw
Philadelphia

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Sir,—Thank you for giving us the opportunity to reply to Dr Bagshaw's letter. His suggestion that our experimental model resembles the early phase of benign essential hypertension is based on experimental work which compared the cardiovascular characteristics of greyhounds and mongrels in the non-anaesthetized, chronically instrumented state [1]. Our greyhounds were anaesthetized, but their resting mean arterial pressure of 106 mm Hg was not dissimiliar to that of his mongrel dogs. Furthermore, we see no reason not to use the greyhound model if "the ability to compensate for perturbations in arterial pressure in the intact greyhound is not significantly different from that of mongrel controls of comparable age and weight". Our previous experimental work on the cardiovascular effects of induced hypotension used greyhounds and formed a valuable basis for comparison [2].

Finally, we wish to add that, in this country, it is understood that animals must be obtained from a reputable supplier or specially bred for experimental purposes. For this reason mongrels would, simply, not have been available to us.

M. R. J. Sury
P. V. Cole
London

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SPINAL ANAESTHESIA WITH BUPIVACAINE

Sir,—We would like to comment on the article by Mitchell and colleagues [1] on effects of posture and baricity on spinal anaesthesia with 0.5% bupivacaine 5 ml. Referring to a study by Chambers, Edström and Scott [2], the authors state that it has been shown that the plain solution of 0.5% bupivacaine is less suitable for abdominal surgery than a hyperbaric solution of bupivacaine. On the basis of their own results, Mitchell and co-workers also state that using 5 ml instead of 3 ml makes the plain solution of bupivacaine more suitable for abdominal surgery.

What Chambers and co-workers demonstrated is that, under the conditions of their study and methodology, the cephalad spread of the plain solution was too low for abdominal surgery. The results of Chambers and co-workers certainly do not warrant the conclusion that the plain solution of 0.5% bupivacaine is less suitable for abdominal surgery. Kalso, Tuominen and Rosenberg [3] showed that, with the patients sitting for 2.5 min after the intrathecal administration of 3 ml, the use of plain 0.5% bupivacaine resulted in increased cephalad spread. Indeed, it has been shown that, provided the patients receiving the plain solution are kept sitting for 2 min or more, the resultant level of sensory blockade after 3 ml is at least the same as when a hyperbaric bupivacaine solution is used [4–6].

Mitchell and colleagues, in their discussion, failed to refer to this earlier work, and merely demonstrated that what has already been shown for 3 ml also applies for 5 ml of 0.5% bupivacaine.

R. Stienstra
J. F. van Poorten
Delft

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Sir,—Thank you for the opportunity to comment upon the letter by Drs Stienstra and van Poorten. We agree that we should have been more specific in our comments regarding the earlier work by Chambers, Edstrom and Scott [1], in that they did not include a "sitting" group in their study with 0.5% plain bupivacaine 3 ml. However, the results of our current study with 5 ml of plain solution did not show any difference in eventual height of block between the "sitting" and "supine" groups, although the onset of the block was faster in the "sitting" group.

We did not have the opportunity to see the paper by Stienstra and van Poorten, which was published after our manuscript was prepared. However, we would point out that this work was performed on a relatively elderly population, while our study and that of Chambers were performed on a much younger population. Care is therefore required in comparing results between such disparate groups, as age is known to be a significant determinant of spread of block in spinal anaesthesia with 0.5% plain bupivacaine [2, 3]. We would also point out that, in this study, the cephalad spread of the block was assessed only up to 20 min. This may not represent the ultimate extent of spread. We assessed our patients to 30 min.

Therefore we maintain that, if a volume of 0.5% bupivacaine 3 ml is to be used in abdominal surgery in younger patients, more reliable results will be obtained with the hyperbaric preparation. If the plain solution is chosen, we would elect to use a volume of 4–5 ml.

R. W. D. MITCHELL
G. M. R. BOWLER
D. B. SCOTT
Leicester and Edinburgh

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TEACHING FIBREOPTIC INTUBATION

Sir,—Dr Ovassapian and his colleagues [1] have described a programme for teaching clinicians the skills required to intubate the trachea using a flexible fibreoptic laryngoscope. Although the programme is effective, Dr Ovassapian has identified several disadvantages inherent in the system, including a considerable amount of time required by instructors and trainees, and the need to obtain informed consent from patients who volunteer to be "simulators." An additional disadvantage not identified by the authors is the risk of injury to the patient volunteers during exposure of the epiglottis and vocal cords by relatively unskilled endoscopists. Also, their programme does not include passage of the fibreoptic laryngoscope through the vocal cords, or advancing the tracheal tube into the trachea of the patient simulator. Ideally, these steps should be practised before using this skill on patients in the clinical setting.

We have developed a teaching programme for fibreoptic tracheal intubation which avoids the problems outlined by Dr Ovassapian. The programme includes a demonstration of the fibreoptic laryngoscope and a description of the intubation technique; individual practice using an intubating mannequin; and finally, fibreoptic tracheal intubation of an anaesthetized, spontaneously breathing pig.

The pig was chosen as the model for this teaching programme because, whilst tracheal intubation in this species is difficult, the airway anatomy resembles that of the human [2]. The mouth is long and narrow; the larynx is small; and the presence of pharyngeal diverticuli makes recognition of the anatomy challenging. In addition, pigs are susceptible to laryngospasm. Therefore, successful fibreoptic intubation of the pig requires recognition of anatomical landmarks, overcoming complications such as excessive salivation and laryngospasm, and manipulation of the fibreoptic laryngoscope through the vocal cords before advancing the tracheal tube into position

This model very closely resembles the clinical situation without the disadvantages described. Time commitments are reduced for instructors and students because several people can be taught simultaneously. Working in this non-stressful environment, students quickly develop confidence in their ability to control and manipulate the fibreoptic laryngoscope before attempting the technique on a patient in the operating room. The advantages are that the anaesthetized pig model is more realistic than use of an intubating mannequin [3]; it eliminates the need for patient volunteers, informed consent is not required, and inadvertent patient injury cannot occur during the practice session.

Use of this model to teach fibreoptic tracheal intubation has met with considerable enthusiasm within our Department and objective evaluation of its effectiveness is underway. It appears to be an efficient and effective alternative to the use of volunteer patient "simulators" for teaching this important skill.

R. FORBES
D. J. MURRAY
Iowa

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USE OF PROPOFOL IN A PATIENT WITH PORPHYRIA

Sir,—In response to a recent article in your journal by Mitterschiffthaler and colleagues [1], reporting the safe use of propofol in a patient with acute intermittent porphyria (AIP), I report a further uneventful use of the drug in this condition.

The patient, a 63-yr-old lady diagnosed several years previously as suffering from porphyria, presented for exploration and repair of a penetrating eye injury. Ten years previously she had been anaesthetized uneventfully for a cholecystectomy, but the notes for this operation were unavailable.

Anaesthesia was induced using fentanyl 0.1 mg and propofol 100 mg. Atracurium 35 mg was given, and the lungs were ventilated with a mixture of 66 % nitrous oxide and isoflurane in oxygen. Arterial pressure, heart rate and ECG were monitored throughout the procedure.

Anaesthesia and recovery proceeded uneventfully and after operation the patient suffered no adverse neurological or vascular sequelae. I believe this to be the third reported use of propofol in porphyria [1,2].

C. McLOUGHLIN
Belfast

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SPINAL ANAESTHESIA AND SURGICAL BLOOD LOSS

Sir,—The literature relating to the influence of anaesthetic techniques on surgical blood loss is sparse and ambiguous. Some reports suggest that induced hypotension and spinal anaesthesia have no effect [1–6], while orthodox opinion remains indifferent to, or unaware of, new evidence.

In a recent prospective study of this subject during large bowel surgery, 47 patients were reported to have lost a mean of 105 (SD 250) ml after spinal anaesthesia, and after inhalation anaesthesia, 51 patients lost 288 (288) ml. The authors concluded that spinal anaesthesia and the associated hypotension, reduced blood loss significantly ($P < 0.001$) [7].

These results were disappointing because they made no contribution to the resolution of the blood loss controversy. Given the range and distribution of their data, the authors used an unspecified method of statistical analysis which appears to have been inappropriate, because these results are incapable of interpretation. Also, insufficient data were published to allow their conclusions to be verified.

These data might have been better presented as a scatter diagram of blood loss plotted against arterial pressure. This simple expedient should demonstrate at a glance any relationship which may exist between these two factors, and its degree. It would also avoid misleading those clinicians who may have only a limited understanding of numbers. Whatever method is used, those of us who have an interest in this field would be most grateful to have these matters clarified.

J. R. DONALD
Glasgow

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Sir,—Thank you for the opportunity of replying to Dr Donald's letter. We cannot agree with Dr Donald that the data regarding blood loss are incapable of interpretation. Figure 1 was included in the paper to demonstrate the distribution of blood loss in the two groups, and shows clearly that the large majority of patients who received spinal anaesthesia had an estimated blood loss of less than 100 ml, while the blood loss exceeded 300 ml in more than 30 % of those who underwent conventional general anaesthesia. The standard deviation was high in the spinal group because one patient had a blood loss in excess of 700 ml. The statistical test used was the Wilcoxon rank sum test, and is entirely appropriate for analysis of data which are not distributed normally. A second figure which showed the distribution of reduction in arterial pressure in the two groups was removed by the editor. However, we do not believe that clinicians who studied figure 1 in conjunction with the values in the text could regard the data as "misleading".

The main purpose of the investigation was to identify any effect of spinal anaesthesia on the incidence of disruption of large bowel anastomoses, and not to resolve "the blood loss controversy".

M. H. WORSLEY
H. Y. WISHART
Glasgow
A. R. AITKENHEAD
Nottingham

The primary purpose of this study was to compare the rate of anastomotic dehiscence following spinal anaesthesia with that following general anaesthesia, and not to determine the mechanism of reduction in blood loss achieved by the former technique; this would have demanded measurements of vascular filling pressures and flow, in addition to mean arterial pressure. The figure which we deleted was a simple graph of distribution of intermittent measurements of systolic arterial pressure by sphygmomanometry; this would not have helped Dr Donald, was irrelevant to the discussion and was therefore deleted.

Although the type of statistical test was not specified in the results section of the paper in question, it was stated clearly in the methods section that three statistical tests were applied "as appropriate", implying that parametric tests would not be used for non-parametric data, as confirmed in the authors' letter.

EDITOR

Br. J. Anaesth. (1989), 62, 116–119

BOOK REVIEWS

Annual Review of Pulmonary and Critical Care Medicine 88/89. Edited by R. A. Matthay, M. A. Matthay and H. P. Weidemann. Published by Hanley and Belfus, Philadelphia. Pp. 201; illustrated; indexed. Price £39.50.

In the 3rd volume in this series, the entire field of pulmonary physiology and medicine from AIDS to weaning is covered in 17 concise chapters. Each comprises a short summary of current areas of interest and abstracts of pertinent papers and comments. The authors are all from the U.S.A. and this is reflected in the choice of papers reviewed. The comments are generally fair, and relevant to clinical practice. The majority of papers reviewed were published in 1986–7 and are thus as topical as possible, bearing in mind the preparation time.

All anaesthetists will find some topic of interest and may also be intrigued by developments in related areas. The volume should find a place in most departmental libraries, although the cost will deter private purchase. The book has hard covers and a high quality of printing. The publishers should be encouraged to consider a less expensive format for a series that, by its nature, has only a limited life, thus enabling more individuals to benefit from the efforts of the authors.

C. D. Hanning

Intensive Care—Pocket Reference. Edited by G. R. Park and A. R. Manara. Published by Castle House Publications Ltd, Tunbridge Wells. Pp. 294; illustrated; indexed. Price £12.95.

It is a difficult task to cover all aspects of intensive care in 294 pages. However, the authors have described concisely the main problems which are likely to confront the junior ITU doctor. There are 20 chapters including, cardiac, respiratory, renal and gastrointestinal disease, fluid and electrolytic problems, shock, poisoning, head injuries and endocrine emergencies.

Each chapter has a brief description of pathophysiology, investigations required and initial management of the condition. There are useful sections on the 11 most common practical procedures, ranging from simple tracheal intubation, to the most complex haemofiltration (although one would hope senior assistance might be sought for the latter). There is a comprehensive up-to-date list of over 150 suggestions for further reading.

Additional aspects of intensive therapy are reviewed in the chapters on sedation and analgesia and microbiology, including Hepatitis B and AIDS. The discussions on Brain Death and Communication in the ITU are very informative and will be of value to all involved in intensive therapy.

The format of this book lends itself to use for quick, easy reference and will appeal to both ITU doctors and nurses. At £12.95 it is likely to be found with the other instant reference books or by the telephone in most units.

T. O'Carroll

Principles of Airway Management, 1st Edn. By B. T. Finucane and A. H. Santora. Edited by D. T. Lowenthal. Published by E. A. Davis Company, Philadelphia. Pp. 277; indexed; illustrated. Price $24.95.

This book, aimed at medical students and various practitioners in many other disciplines including anaesthesia, falls between two stones. On the one hand, some chapters are basic but very well illustrated, while others would either frighten the young reader or baffle the tyro with many complicated syndromes that may cause difficulty with intubation. The chapters that are well worth reading are those on anatomy, cardiopulmonary resuscitation, airway management and most of the aspects of intubation. I was pleased indeed to find that confirmation of successful intubation was included and very well covered. I particularly enjoyed the chapter on the paediatric airway. It is alarming that the problems following damage to lips and teeth in adults have caused such a large number of legal problems in the U.S.A. It is also interesting that the "tooth fairy" also exists "over there" in children but, no doubt, at considerably increased sums!

There are two major errors in chapter 5, where two diagrams are labelled incorrectly. These should be corrected as a matter of urgency.

I was disappointed that two messages were absent. The first is that patients do not die from failure to intubate, but from failure to oxygenate. Second: "when in doubt, take the tube out."

In summary, this book has some superbly illustrated, short, concise chapters for medical students and young practitioners. Others, I think, are for the more advanced practitioner. I do not think it will be popular in the United Kingdom, as I believe there are other books available.

R. S. Vaughan

Introduction to Anesthesia: The Principles of Safe Practice, 7th Edn. By R. D. Dripps, J. E. Eckenhoff and L. D. Vandam. Published by W. B. Saunders Company, London and Philadelphia. Pp. 484; illustrated; indexed. Price £18.50.

A "double-take" is induced by the first sight of this book. Whilst it is not uncommon for a long deceased author of a famous book to live on in the title of new editions (think of *Gray's Anatomy*, for example), it is uncommon to mix the living and the dead on the cover. One of the three "authors" of this 7th edition is dead and the other two are Emeritus Professors. They are obviously very much alive, despite being assisted in writing this book by 21 other contributors. It is a tribute to the sense of style which has always characterized this book that it is impossible, merely by reading a chapter at random, to guess whether it is by one of the original authors or by one of the new contributors. The "old hands" have obviously put in a lot of effort, both in updating their own chapters and in the editorial work on the other contributions to this new edition.

The short opening section on Broad Perspectives views the field through American eyes, but nevertheless purveys some perceptive general truths on such matters as the relationship between surgeons and anaesthetists. The next three sections take the reader along the obvious sequence of Essential Preanesthetic Considerations, Anesthesia and Operation, and Ancillary Care. Anesthesia and Operation is sub-divided into six parts, some of which (in common with Regional Anesthesia) contain logically grouped chapters, but some of which are more akin to a portmanteau.

Despite its American origin, the book is valuable as a textbook in any medical environment. In the days when medical students were expected to learn anaesthetics, it was widely recommended: it has now moved up the educational scale and is an excellent text for all postgraduate trainees. It is not verbose: sufficient basic science is always included to justify every recommendation and it is really up-to-date. It includes, for example, a very clear guide to fibreoptic intubation. It is also extremely comprehensive, considering its size and price. The writing is unfussy and the authors are not afraid to give a didactic opinion. One can thoroughly recommend it to any trainee.

M. D. Vickers

Diamorphine: Its Chemistry, Pharmacology and Clinical Use. Edited by D. B. Scott. Published by Impulse Sales Promotion Ltd, London. Pp. 123; indexed; illustrated. Price £27.50.

There are several drugs, long-established in medical practice, which have not had to face the obstacles presented by either the Committee on Safety of Medicines or the Food and Drug Administration. Diamorphine is one such drug, which achieved popularity during the first half of this century. However, because of the dangers of abuse and physical dependence, it was banned from medicinal use in the United States of America in 1924 and with few exceptions most other countries followed this example. Consequently, diamorphine has not been subjected to the battery of detailed investigation and controlled clinical studies now required of new drugs and its use is dependent frequently on personal experience and opinion. Thus studies on this drug are relatively scarce and dispersed throughout the medical journals.

This small book, commissioned by Evans Medical Ltd, fills a gap in the literature by reviewing succinctly the available data on diamorphine and its role in clinical practice. It comprises eight short chapters on chemistry, pharmacokinetics and pharmacodynamics, the use of diamorphine in acute and chronic pain, the use of diamorphine by extradural and subarachnoid routes and the problems of overdosage and physical dependence.

Each chapter is well-structured, some illustrated by large, clear line diagrams and aimed at a broad general audience. For some anaesthetists, much of the information would be well-known; experts in the field of opioids would not need to refer to this text. Nonetheless, it provides a summary of information which cannot be obtained elsewhere in such a concise form and it is recommend thoroughly as a starting point for anaesthetists who wish to further their knowledge of diamorphine; it will serve as a useful monograph for other physicians and pharmacists.

G. Smith

Care of the Critically Ill, 3rd Edn. Edited by S. M. Ayres, R. Schlichtig and M. J. Sterling. Published by Year Book Medical Publishers, Chicago. Pp. 425; illustrated; indexed. Price £25.

Medical writing on critical care tends to fall into one of two categories: the comprehensive textbook, or the restricted monograph. This book appears to occupy a middle position, and its title may therefore mislead. It may be described best as a textbook of applied physiology in the critically ill.

The authors concentrate throughout on basic mechanisms of normal and disordered physiology, with particular reference to the factors which influence oxygen delivery to the tissues. The greater proportion of the book is devoted to cardiovascular and respiratory system function, and the relationship between sepsis and multiple organ failure; concentrating on these important areas is entirely appropriate, but it leaves the text unbalanced. Only one chapter is devoted to the whole subject of renal function, fluid and electrolyte balance, and i.v. fluid management; detail is necessarily brief.

Indeed, there are several surprising omissions in this book, some of which may be explained by the American perspective and the emphasis on physiology. There is little discussion of practical patient management, and the junior doctor will find little didactic advice on problems such as when to intubate the trachea of a patient, what fluids to use, how to determine the cause of acid–base abnormalities, methods of central cannulation, and so on. No mention at all is made of methods of sedating the critically ill patient, of the use of neuromuscular blocking drugs, or of the effect of renal failure on cumulation of opioid metabolites. Tracheal intubation is described as an awake procedure, and the authors do not appear to have considered the use of i.v. anaesthesia. Methods to prevent renal failure are inadequately emphasized, and there is no description of chronic arteriovenous haemodialysis, a technique which is tending to supplant simple haemofiltration and formal haemodialysis in the U.K. References to European research are scanty, and no mention is made of selective decontamination of the gastrointestinal tract; this is a technique which has been largely disregarded by the American intensivist.

The strength of this book is its excellent description of physiology in the critically ill, and many important areas such as catheter sepsis, the role of the gut, and the importance of severity scoring are clearly emphasized. The price is well within the bounds of most intensive care units, and I strongly recommend it as a physiological text to be used in conjunction with other books by European authors.

J. F. Bion

Medicine for Disasters, 1st Edn. Edited by P. Baskett and R. Weller. Published by Butterworth & Co. (Publishers) Ltd. Pp. 294; indexed; illustrated. Price £60.00.

The title of this book reflects an approach to an extensive subject which is covered badly in current literature. The 33 contributors are not only listed, but their experience in this field is documented uniquely in eight pages of biographies. Although they are obviously an experienced and knowledgeable group, we were disappointed that their number did not include more individuals with first hand "on the ground" knowledge of any of the major disasters of the past decade.

The book is well set out, the first section being a thorough review of the evolution of medical practice during disasters throughout history. This is followed by sections on the immediate and the continuing phases of dealing with disasters. The final section devotes a chapter to each specific type of disaster—both natural and man-made.

The chapters in the immediate phase of care deal with topics of triage, immediate resuscitation (an excellent outline) and analgesia/anaesthesia in the field. In addition to these overtly medical subjects, management issues such as assessment of disasters, planning, co-ordinating relief and training of personnel are discussed in detail. This section has obviously been written by contributors who have a good working knowledge of the practical problems which occur. The appendix to Chapter 9, a series of case histories to which the reader can apply his triage abilities, is fun.

One inaccuracy in Chapter 4 concerns the muscle relaxant alcuronium. Few experts in the field of neuromuscular blockade would accept this drug as a short acting agent compared with vecuronium or atracurium.

The section on the continuing phase covers not only medical aspects of care and principles of patient evacuation/dispersal, but also public relations, the media and the psychological effects of a major disaster on survivors and medical/paramedical staff.

The final section dealing with specific disasters is comprehensive. Although every disaster situation cannot be discussed in any single work, this book sets out many situations in sufficient detail and gives the reader a "feel" for what is important in planning medical care after a disaster. This section is also most illuminating from a general knowledge stand point. Does the reader know that tidal waves are termed more correctly "tsunami" as they have nothing to do with tidal forces? Is the reader familiar with their periodicity and the innocent way in which they begin? Some of this information may be useful at sometime in the future. It is reassuring to know that the ground floor is the place to be during an earthquake; and that a Pacific beach on which fish are suddenly being left "grounded" because of a sudden reduction in water level may not be as innocent as it appears. The section on volcanoes makes extensive use of data derived from the eruptions of Mount St Helens in 1980.

The chapters dealing with man-made disasters close the book. Those dealing with nuclear accidents are of particular interest. The incidents at Three Mile Island and Chernobyl are described in detail, without the exaggeration and inaccuracy which typified the immediate media coverage.

The conclusions drawn in respect of road traffic accidents are not new; we require better and quicker response by medical/paramedical staff, with more aggressive treatment at the scene.

All in all, this is a well written, practical book. The chapters are referenced adequately for those wanting to read more deeply. It contains many well accepted concepts, together with newer recommendations which it supports with well documented practical experiences. Its major function, however, is to draw together information which hitherto has been scattered among a wide variety of publications and disciplines.

This is not a book for rapid reference and, although sections such as that dealing with immediate resuscitation would be of great value to medical students and early postgraduates, it is clearly aimed at senior medical, administrative and government personnel. It is a book which should be available in all Accident & Emergency Departments and major Intensive Care Units, and especially in the offices of those individuals who control overall planning and allocation of resources within the Health Service.

D. L. Coppel
G. G. Lavery

Anaesthesia Review 5. Edited by L. Kaufman. Published (1988) by Churchill Livingstone, Edinburgh, London, Melbourne and New York. Pp. 344; indexed; illustrated. Price £17.50.

In his fifth set of reviews, Dr Kaufman gives us 18 main topics dealt with by 22 authors and four updating briefs on medicine and anaesthetic topics prepared by himself. The reviews are an interesting mixture of basic sciences (e.g. the autonomic nervous system and the sites of action of opioids in the nervous system), pathophysiology (e.g. cerebral ischaemia and ARDS) and clinical anaesthesia (e.g. ENT, ophthalmic, dental and cardiac anaesthesia).

The reviews are well written, well-referenced and up to date. Whilst it is invidious to compare them, I particularly enjoyed Adams' review of the psychiatric sequelae of surgery and Yaksh's review of the actions of opioids.

The whole collection will be useful to almost all anaesthetists. Those taking Part III F.F.A.R.C.S. will be well served—as well as their teachers and trainers.

J. Norman

Recent Advances in Critical Care Medicine, Volume 3. Edited by I. McA. Ledingham. Published by Churchill-Livingstone, Edinburgh. Pp. 215; indexed; illustrated. Price £29.50.

In the 5 years since the publication of the last volume in this series, there has been considerable progress in the field of Intensive Care Medicine. This has been paralleled by a perceived need to justify vigorously decisions to use new, expensive therapeutic and diagnostic techniques. The third volume of *Recent Advances in Critical Care Medicine* reflects these changes and, with contributions from clinicians and researchers who are acknowledged leaders in their fields, maintains the high standard of previous volumes.

Volume three succeeds in presenting an overview of important developing clinical areas, in addition to more detailed discussion of advances and controversies in areas of basic scientific research.

The opening chapter places in perspective the role of outcome prediction and is a review of the experience of Knaus and Zimmerman in Washington with the APACHE II scoring system. The authors emphasize that such prognostic scores should not be applied to individual patients, but suggest that they can be useful in conjunction with clinical judgement when deciding on complex treatment strategies.

The next three contributions deal with topics related to respiratory intensive care. New and old methods of weaning from mechanical ventilation are discussed and contrasted, with emphasis on the impact of such processes on the work of breathing and ventilatory muscle fatigue. Discussion of the perennial problem of acute respiratory failure in patients with chronic obstructive pulmonary disease rationalizes a logical approach to these patients, stressing the importance of prevention of acute respiratory failure. Dr Perret's excellent overview of asthma includes mention of the widely accepted technique of mechanical, controlled hypoventilation in status asthmaticus, described originally from his department.

Chapter 5 deals with the changing face of sedative practice in intensive care, a topic that was included in the last volume. The editor felt a further update was necessary and this chapter reflects the changes in attitude that have occurred in the U.K. Diagnosis and management of bleeding disorders in the critically ill includes a description of normal haemostasis followed by a lucid, well-balanced discussion of the causes of bleeding in such patients, with an update on the aetiology, pathophysiology, laboratory diagnosis and treatment of disseminated intravascular coagulation.

A short chapter emphasizing the importance of right ventricular dysfunction in pulmonary embolism and adult respiratory distress syndrome represents the only contribution on cardiovascular problems. The authors rationalize the place of noradrenaline in the management of right ventricular failure based on canine studies and clinical experience.

A review of current thoughts on sepsis, hypermetabolism and multiple organ failure puts into perspective the place of metabolic support and is followed by a contribution from Groningen describing the pathogenesis of Gram-Negative infection in the ICU. This includes a review of the therapeutic approaches to hospital acquired infection and the authors' experience with the controversial concept of selective decontamination of the digestive tract.

The next two chapters relate to research developments and include a presentation of the clinical and experimental evidence for the persistent effects of sepsis and injury on thermoregulation and a review of the role of endogenous opioid peptides in shock.

The final chapter, on recent advances in the management of acute renal failure, presents a wealth of information in a few pages. It contains a useful algorithm on the treatment of oliguria and describes the place of dopamine and diuretics. The description of the various combinations and forms of arteriovenous haemofiltration with haemodialysis and plasmaphoresis and the uses and indications of these techniques is confusing because of its brevity.

Volume 3 maintains the paramount reputation of this series as a source of "state of the art-update" information for practitioners of Intensive Care Medicine. In this edition, the choice of contributions and contributors cannot be faulted—the result of the high standards of the Editor. This volume, in common with its predecessors, should be purchased by all involved in Critical Care Medicine.

D. A. B. Turner

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"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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EDITORIAL

CISAPRIDE AND ANAESTHESIA

Cisapride (R 51 619, Janssen Pharmaceutica) is a gastrointestinal prokinetic drug currently undergoing clinical trials. It is a derivative of cis-4-amino-3-methoxypiperidine and has many properties that may be of interest to the anaesthetist.

Cisapride increases lower oesophageal sphincter (LOS) pressure in both conscious volunteers and patients [1, 2]. It increases the rate of gastric emptying [3] and reverses the morphine-induced delay in gastric emptying in patients before anaesthesia [4, 5]. However, the rate of production and composition of gastric secretions are not affected by cisapride [6]. The drug also increases the motility of both the small and large intestines [7, 8].

There are several pharmacological differences between cisapride and the presently available gastrointestinal prokinetic agents metoclopramide and domperidone. Unlike these agents, cisapride has no anti-dopaminergic properties [9]. Consequently, extrapyramidal side-effects, a frequent problem with metoclopramide [10], have not been reported. Animal studies have shown that cisapride acts predominantly by enhancing the release of acetylcholine from the nerve endings in the myenteric plexus in the wall of the gastrointestinal tract [11]. The reversal of morphine-induced delay in gastric emptying by cisapride is of considerable interest, and the action of cisapride in this respect has been compared directly with metoclopramide in patients before surgery [5]. In this study, it was shown that cisapride was considerably more effective than metoclopramide. Finally, unlike metoclopramide and domperidone, cisapride enhances large bowel motility [8].

Cisapride has been administered by mouth, i.m., i.v. and rectally. The bioavailability of oral cisapride is 40–50% because of first-pass metabolism, with peak concentrations in the plasma at 1–2 h and an elimination half-life of 7–10 h in healthy subjects [12]. Absorption after i.m. administration is rapid and reliable [4]. An improved rectal formulation has been developed more recently. This cyclodextrine-based suppository is absorbed rapidly and therapeutic concentrations are maintained for at least 9 h [13].

The principal uses for cisapride are likely to be in the treatment of reflux oesophagitis [14], syndromes of delayed gastric emptying [15], intestinal pseudo-obstruction [16], functional post-prandial dyspepsia [17] and constipation [18]. What, therefore, is the potential for cisapride in anaesthetic practice?

The results of an important study of the possible use of cisapride in anaesthesia are published in this issue of the *British Journal of Anaesthesia* [19]. This study has investigated the effect of cisapride on LOS pressure when it was given before antagonism of neuromuscular blockade with atropine and neostigmine. Cisapride increased LOS pressure significantly before antagonism, but failed to prevent the decrease in LOS pressure after administration of atropine and neostigmine. These results are disappointing, as Corazziari and colleagues [20] found that cisapride increased oesophageal motility and LOS pressure in patients with oesophageal reflux and that atropine reversed the effects on peristalsis but had no effect on the increased LOS pressure. However, the patients in this study were not under anaesthesia. Cisapride may be useful, therefore, before induction of anaesthesia, especially in patients with reflux oesophagitis, but it has now been demonstrated that it will not be effective after antagonism of neuromuscular blockade with atropine and neostigmine [19].

It has been established that cisapride prevents the delay in gastric emptying caused by morphine [4, 5]. Cisapride seems to be unique in this respect. There have been no reported studies on the delay in gastric emptying produced by other opioids, but it would be surprising if cisapride did not have the same effect. The inhalation of gastric contents is an important cause of anaesthetic mortality associated with surgery and obstetrics [21, 22] and the use of opioids before induction of anaesthesia probably makes inhalation more likely [23]. The preoperative use of cisapride, especially in emergency and obstetric anaesthesia, may well reduce the incidence of this complication. However, there are no data available at present on the effect of cisapride on the progress of labour and the condition of the neonate.

There is no current evidence of an effect on nausea and vomiting associated with anaesthesia. Postoperative gastric stasis may cause nausea and vomiting and it has been shown that cisapride is effective in the treatment of post-prandial nausea associated with gastroparesis [24]. The possible anti-emetic effect of cisapride is currently being investigated in animals. Gastric stasis may be an important cause of postoperative nausea and vomiting and cisapride may well be useful in this situation. However, this is only speculative, as clinical studies have not yet been performed.

The enhancement of gastrointestinal motility caused by cisapride may affect the absorption of drugs administered by mouth. For example, the rate of absorption of cimetidine and diazepam has been shown to be increased in patients receiving cisapride [12, 25]. This may be beneficial in the absorption of oral analgesics and studies are currently addressing this question, while others are examining the effect of cisapride on the absorption of oral paracetamol and opioids. Because of its effect on opioid-induced delay in gastric emptying, cisapride may be beneficial in the treatment of constipation caused by chronic opioid therapy. Studies investigating this problem are also in progress.

Gastrointestinal stasis is a common problem in patients in intensive therapy. There are no plans at the moment to investigate the use of cisapride in this situation, as the safety of a new drug should be established before it is used in the intensive therapy unit. Premature infants, intolerant of oral feeds associated with marked gastric stasis, have been treated successfully with cisapride [26].

Because of the adverse events associated with the i.v. administration of domperidone [27] and the peripheral vasodilating action of i.v. cisapride [25], caution is necessary in the use of the parenteral preparation of cisapride. It is recommended that parenteral cisapride should be given i.m.; if i.v. administration is essential, the drug should be given as a dilute solution slowly over 3 min [19]. At present, there are no plans to apply for a licence for the use of parenteral cisapride.

In conclusion, cisapride may well have a role to play in future anaesthetic practice, but considerably more investigation is needed. If cisapride is to be available for general use only as an oral preparation, its use in anaesthesia will be limited. However, the new rectal preparation is a promising development, as it may be a satisfactory method of administration of the drug in anaesthetic practice and the intensive therapy unit.

D. J. Rowbotham

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EFFECTS ON THE LOWER OESOPHAGEAL SPHINCTER OF CISAPRIDE GIVEN BEFORE THE COMBINED ADMINISTRATION OF ATROPINE AND NEOSTIGMINE

M. J. JONES, R. W. D. MITCHELL AND N. HINDOCHA

The lower oesophageal sphincter (LOS), is the major physiological barrier to gastro–oesophageal reflux [1]. Consequently, any drug which decreases LOS tone may be expected to increase the possibility of regurgitation, whereas drugs that increase LOS tone may be expected to reduce this risk. The overall resistance to gastro–oesophageal reflux is represented by the barrier pressure (BrP)—the pressure differential between the LOS and the stomach (BrP = LOS pressure minus gastric pressure (GP)).

Atropine or glycopyrrolate in combination with neostigmine are frequently used to antagonize the residual effects of neuromuscular blockade at the termination of surgery. Previous studies [2,3] have observed that LOS pressure and BrP decreased significantly following the administration of these drugs. Although metoclopramide causes a marked increase in BrP, it does not antagonize this adverse effect of anticholinergic agents [4]. Unfortunately, the i.v. preparation of domperidone, which was more effective in this respect [5], has been withdrawn from the U.K. market following observation of arrhythmias.

Cisapride (R51 619, Janssen Pharmaceutica) is a new gastrointestinal prokinetic drug [6]. Unlike metoclopramide or domperidone, it is devoid of antidopaminergic or direct cholinergic effects and appears to act primarily by enhanced release of acetylcholine at the myenteric plexus [7].

The present study was designed to investigate if cisapride (which is known to increase LOS pressure [8–10]), when given before the simultaneous administration of atropine and neostigmine, antagonizes the effects of the anticholinergic on BrP.

SUMMARY

Twenty healthy female patients undergoing laparoscopy were allocated randomly to receive either cisapride 10 mg i.v. in 5% dextrose 20 ml or placebo 15 min before antagonism of residual neuromuscular blockade with atropine 1.2 mg and neostigmine 2.5 mg. Barrier pressure (BrP = lower oesophageal sphincter (LOS) pressure minus gastric pressure) increased significantly (by 25%) following cisapride, but not placebo, within 10 min of injection; following the combined administration of atropine and neostigmine, there was an abrupt decrease in mean BrP in the cisapride group from 37.0 (SEM 4.5) cm H_2O to 24.1 (3.2) cm H_2O ($P < 0.01$) and in the control group from 26.6 (4.8) cm H_2O to 19.9 (3.1) cm H_2O ($P < 0.05$) 2 min after injection. Subsequently, there was a small increase in BrP to values not significantly lower than control measurements. Thus the administration of cisapride before antagonism of neuromuscular blockade with atropine and neostigmine failed to block the adverse effect of atropine on the LOS.

PATIENTS AND METHODS

Twenty healthy female patients undergoing laparoscopy gave informed consent to participate in the study, which was approved by the District Ethics Committee. All patients were devoid of gastrointestinal disease and were not receiving any drug therapy.

Each patient received a standardized anaesthetic technique consisting of premedication with diazepam 10 mg by mouth 2 h before operation, induction with thiopentone 4 mg kg^{-1} and alcuronium 0.3 mg kg^{-1} to facilitate tracheal intubation and artificial ventilation. Anaesthesia

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This article is accompanied by an Editorial.

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was maintained with 70% nitrous oxide and 0–1% enflurane in oxygen, supplemented with 10 mg morphine i.v.

Measurements of lower oesophageal sphincter pressure (LOSP), oesophageal pressure (OP) and gastric pressure (GP) were performed by manometry as described in detail in previous publications from this department [1,2]. In brief, when a stable anaesthetic state had been achieved, the oesophageal manometry tube was passed through the patient's mouth until all three pressure transducers were in the stomach. The tube remained *in situ* for approximately 15 min, to allow gastric motility to return to normal before pressure recordings were made. Measurements of GP, LOSP and OP were made at end expiration by a "pull through" manoeuvre.

On completion of surgery, and with the patient in a horizontal, supine position, three control measurements of GP, LOSP and BrP were made. Subsequently, patients were allocated randomly to receive either cisapride 10 mg in 5% dextrose 20 ml given i.v. slowly over 3 min, or 5% dextrose 20 ml i.v. (placebo). Non-invasive monitoring of arterial pressure at 1-min intervals and continuous ECG recording were performed during the administration of cisapride. Further pull through manoeuvres were performed at 5, 10 and 15 min after cisapride or placebo, then atropine 1.2 mg and neostigmine 2.5 mg were given in combination as a bolus injection i.v. and further measurements of GP, LOSP and BrP performed at 1-min intervals for 10 min. During and after antagonism of neuromuscular blockade, anaesthesia was maintained with 70% nitrous oxide

TABLE I. *Patient characteristics (mean (SEM))*

	Age (yr)	Weight (kg)
Cisapride group ($n = 10$)	30 (2)	68 (3)
Placebo group ($n = 10$)	33 (2)	63 (3)

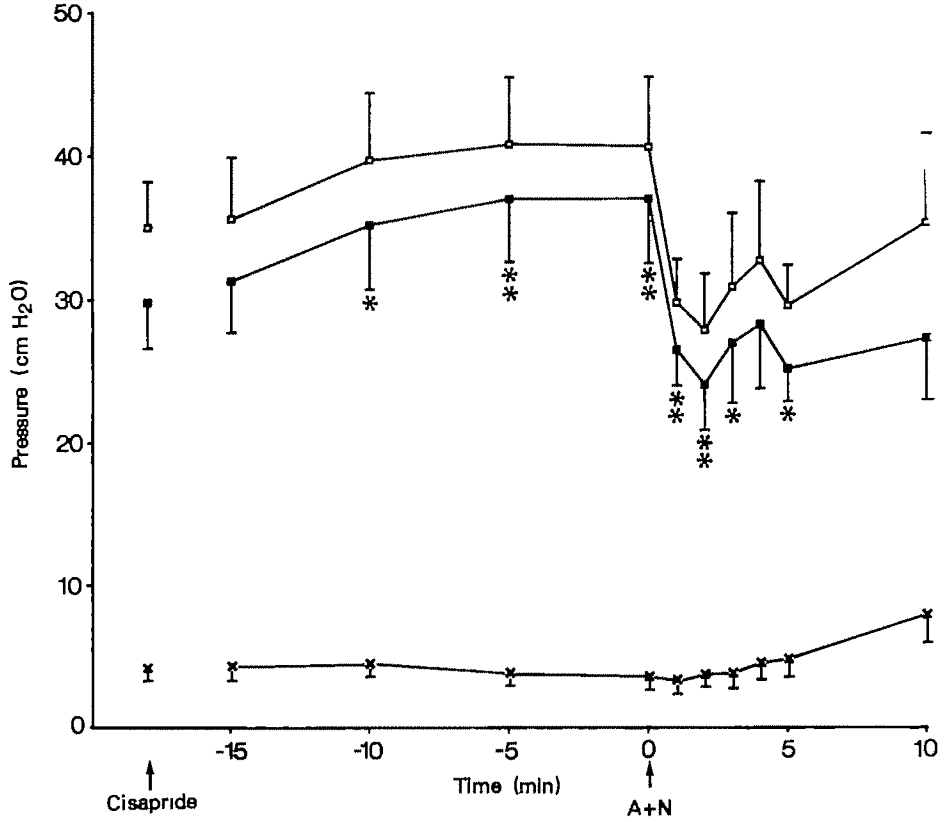

FIG. 1. Effects of cisapride 10 mg followed by simultaneous administration of atropine 1.2 mg and neostigmine 2.5 mg (A+N) on lower oesophageal sphincter pressure (□), barrier pressure (■) and gastric pressure (x). Mean values (SEM); $n = 10$. *$P < 0.05$; **$P < 0.01$.

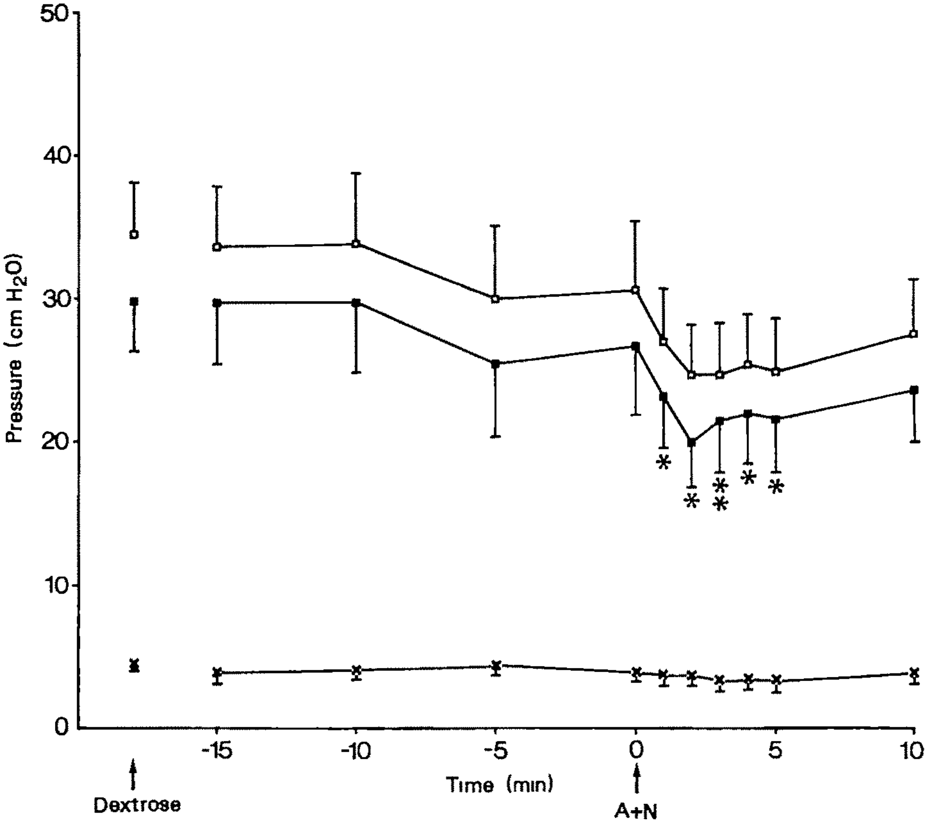

FIG. 2. Effects of placebo (5 % dextrose) followed by simultaneous administration of atropine 1.2 mg and neostigmine 2.5 mg (A+N) on lower oesophageal sphincter pressure (□), barrier pressure (■) and gastric pressure (x). Mean values (SEM); $n = 10$. $^{*}P < 0.05$; $^{**}P < 0.01$.

and 0–1 % enflurane in oxygen to prevent straining or coughing.

Results were analysed statistically using analysis of variance, followed by Student's *t* test for paired and unpaired data as appropriate.

RESULTS

There was no significant difference in mean age and weight of the patients in the two groups (table I).

Following the administration of cisapride there was an increase in mean BrP from 29.8 (SEM 3.2) cm H_2O to 35.2 (4.5) cm H_2O ($P < 0.05$) 5 min after the end of injection, and a further increase to 37.0 (4.5) cm H_2O ($P < 0.01$) after 10 min (fig. 1). This increase was maintained up to the time of administration of atropine and neostigmine. In contrast, there was no significant change in BrP in the placebo group during this 15-min interval (fig. 2).

Following the simultaneous administration of atropine 1.2 mg and neostigmine 2.5 mg, in the cisapride group mean BrP decreased to 26.5 (2.5) cm H_2O at 1 min ($P < 0.01$), with a further decrease to 24.1 (3.2) cm H_2O at 2 min, which was lower than control values ($P < 0.05$). After 10 min ($n = 7$) BrP had increased to 27.3 (4.3) cm H_2O, a value not significantly different from that measured before antagonism of neuromuscular blockade.

In the placebo group, after atropine and neostigmine there was a decrease in BrP from 26.6 (4.8) cm H_2O to 23.1 (3.6) cm H_2O at 1 min ($P < 0.05$), with a further decrease to 19.9 (3.1) cm H_2O after 2 min ($P < 0.05$). BrP remained significantly below the value before antagonism of motor blockade for a duration of

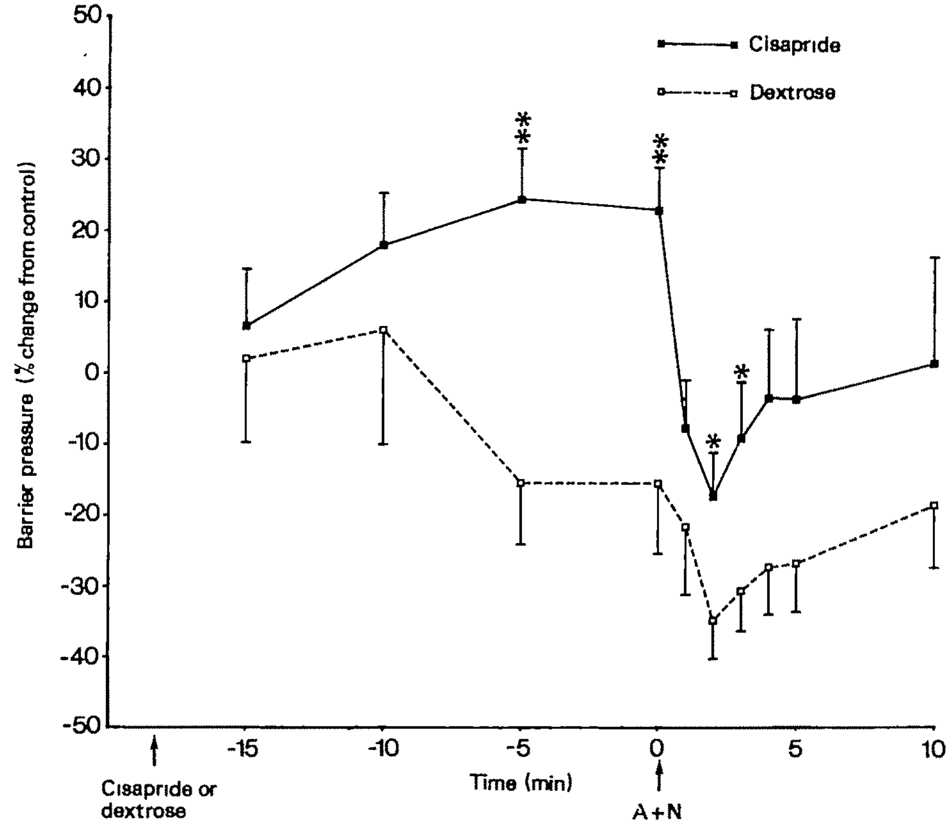

FIG. 3. Comparison of barrier pressure (as percent change from control values) between patients receiving cisapride 10 mg or placebo, followed by the simultaneous administration of atropine 1.2 mg and neostigmine 2.5 mg (A+N). Mean values (SEM). $*P < 0.05$; $**P < 0.01$.

5 min, after which further measurements performed at 1-min intervals did not reveal any significant differences.

A comparison of BrP between the two groups is shown in figure 3. Calculated as a percentage change from control values, there was a significant difference between the groups ($P < 0.01$) 10 and 15 min after the administration of cisapride or placebo. Following administration of atropine and neostigmine, there was a reduction in both groups, although cisapride provided a small but significant ($P < 0.05$) sparing effect 2 and 3 min after injection. There was no difference in final BrP values either between groups or from control values.

There was no difference in arterial pressure or heart rate between the two groups at any time.

DISCUSSION

Our results confirm previously reported observations [8–10] that cisapride increases LOSP and is likely, therefore, to result in a decreased tendency to regurgitation [1]. However, the combined administration of atropine and neostigmine to antagonize neuromuscular blockade produced an immediate abrupt decrease in LOSP and BrP following cisapride. We found no significant difference in the final measurement of barrier pressure between subjects given cisapride or placebo, indicating that cisapride, in the recommended clinical dose, does not antagonize the deleterious effect of atropine on the LOS. Although no adverse cardiovascular effects were observed in this study it is usually recommended that cisapride be administered i.v. slowly, as bradycardia has been reported.

Previous attempts to prevent the decrease in LOSP and BrP caused by atropine have concentrated on the use of dopamine antagonists, such as metoclopramide or domperidone. Whilst the mechanism of action of cisapride is not entirely clear, it does not appear to depend upon cholinergic or antidopaminergic properties. Cisapride is devoid of stimulatory effects on gastrointestinal secretions and it does not induce neuroendocrine effects or dystonic reactions characteristic of a dopamine receptor antagonist [7]. Consequently, it has been suggested that cisapride may be a useful agent in the prevention of gastrointestinal reflux [11]. The combined beneficial effects of increased BrP, enhanced gastric emptying [12, 13] and absence of increased gastrointestinal secretions [7], suggests that cisapride may be valuable in emergency or obstetric anaesthesia to prevent gastro–oesophageal reflux.

In conclusion, our study has found that cisapride increased LOSP significantly, but the increase in BrP was attenuated by the subsequent use of atropine, and the latter drug exerted a predominant effect. There remains the necessity to protect the airway following administration of atropine and neostigmine when given to antagonize neuromuscular blockade during general anaesthesia.

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EFFECTS OF GENERAL ANAESTHESIA WITH HALOTHANE ON ANTRODUODENAL MOTILITY, pH AND GASTRIC EMPTYING RATE IN MAN

B. A. SCHURIZEK, L. H. O. WILLACY, K. KRAGLUND, F. ANDREASEN AND B. JUHL

SUMMARY

Antroduodenal motility, pH and gastric emptying rate were measured in 11 patients undergoing orthopaedic or plastic surgery with general anaesthesia. Motility was measured by manometry and gastric emptying rate by the rate of paracetamol absorption. During anaesthesia, gastric emptying was delayed in eight patients. General anaesthesia with halothane reduced the duration of the interdigestive motility complex ($P < 0.01$), mainly by a shortening of phase II ($P < 0.01$) which correlated with the inhaled concentrations of halothane ($P < 0.01$). Anaesthesia impeded the occurrence of antral contractions during phase II ($P < 0.01$); the frequency of contractions was unchanged during anaesthesia, but decreased during the recovery period ($P < 0.01$). The amplitudes of antral contractions diminished with anaesthesia ($P < 0.01$), but increased after operation. The frequency of contractions in the duodenum was unchanged during phase II and reduced during phase III ($P < 0.01$). Gastric pH increased during and after operation ($P < 0.01$). General anaesthesia with halothane affects gastroduodenal motility especially during phase II, increases gastric pH and delays gastric emptying rate.

Acid aspiration continues to be one of the main factors in mortality and morbidity associated with general anaesthesia [1–3]. There is little information on the effects of anaesthetic drugs on gastrointestinal motility and gastric emptying rate in the perioperative period. An increase in the volume of acid gastric contents because of reduced gastroduodenal motility is likely to increase the risk of inhalation of these contents in the perioperative period [4].

In the fasting human, gastric and small bowel motor activity is a cyclic phenomenon, periods of contractile activity alternating with periods of quiescence. This pattern of motility, which has been termed the interdigestive motility complex (IDMC), is divided into three phases: periods of quiescence (phase I), followed by persistent irregular contractile activity (phase II) which is replaced by a short period of regular contractions (phase III). The IDMC empties the stomach and the small bowel from residual and fasting contents; its duration is approximately 2 h [5].

In animals, halothane has been found to abolish or to reduce phase III activity [6–8], but no information was given on antral motility or gastric emptying rate.

This study has investigated the effects of general anaesthesia with halothane on antroduodenal motility, pH and gastric emptying rate in the perioperative period in man. Antroduodenal motility was measured using the manometry method [5, 9], and gastric emptying rate using the rate of absorption of paracetamol [10–12].

PATIENTS AND METHODS

Patients

We studied 11 patients (five male) aged 27–59 yr who were without clinical evidence of gastrointestinal or other systemic disease and who were

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undergoing orthopaedic or plastic surgery not involving the abdomen. The estimated duration of anaesthesia was 2 h. None of the patients was a regular user of any drug known to influence gastroduodenal motility or gastric pH. Informed consent and Ethics Committee approval were obtained.

Gastrointestinal motility and gastric pH

Antroduodenal motility was recorded by means of a six-channel polyvinylchloride tube (o.d. 4.7 mm) (GIMK-14R7-250 A, William Cook Europe A/S) The manometric assembly, complete with a pH electrode, was passed through a nostril and placed, under fluoroscopic control, so that the tip was near to the ligament of Treitz.

Each channel of the manometric tube had an inner diameter of 0.7 mm and a side hole opening of 0.7 mm sited at various distances from the tip. Side openings at 2, 18, 34 and 42 cm from the tip of the tube were arranged so that two were placed in the gastric antrum (A1 proximal and A2 distal) and two in the duodenum (D1 proximal and D2 distal). The lumina were perfused continuously with distilled water at a rate of 0.2 ml min^{-1} per channel, utilizing a pneumohydraulic capillary infusion system (Kraglund, William Cook Europe A/S). Intraluminal pressure activity was measured by strain gauge transducers (Gould–Statham physiological pressure transducer) and recorded on a multi-channel paper chart recorder (Mingograf 805, Siemens Elema, Sweden).

The pH microelectrode (GK 2801-C, Radiometer, Copenhagen, Denmark) attached to the side of the manometric catheter was located between the two antral recording sites. It was calibrated with commercial buffer solutions (pH 4.01 and 1.09). Gastric antral pH was displayed continuously on a pH meter (pH-meter 75, Radiometer, Copenhagen, Denmark) and recorded on the paper chart recorder. All investigations were recorded via an interface on a multichannel tape recorder (TEAC XR-510) for later data compression and analysis.

Gastric emptying rate

The rate of gastric emptying was assessed by measuring the rate of absorption of paracetamol administered by mouth.

Procedure

All patients were premedicated with diazepam (Stesolid tablets), 10–20 mg according to age and weight, given at 6 a.m. All investigations started at 7 a.m. When the manometric/pH assembly was positioned as described above, the preoperative antroduodenal motility and pH were measured.

Immediately before induction of anaesthesia, each patient received paracetamol 20 mg kg^{-1} (median 19.6 mg) (whole and half 500-mg Panodil tablets with 20 ml of water). Induction of anaesthesia was with thiopentone after pethidine 30–50 mg and pancuronium 0.75–1.0 mg had been given. Tracheal intubation was facilitated with suxamethonium 75–100 mg. Anaesthesia was maintained with halothane and 67% nitrous oxide in oxygen. Pancuronium and pethidine were given if required. Anaesthesia was not standardized, but was adjusted to the requirements of the patient and the operation. At the end of surgery, neuromuscular blockade was antagonized with neostigmine 2.5 mg given with atropine 1 mg. All patients were anaesthetized by the same staff. Following anaesthesia, the patient was observed in the recovery room and analgesics were given when needed.

Blood samples were obtained, for measurement of serum paracetamol concentrations, at 15, 30, 60 min and 1.5, 2.5, 3.5, 4.5, 5.5, 8, 12 and 24 h after ingestion of the drug. The serum was separated immediately and stored frozen. Antroduodenal motility and gastric pH were measured continuously except during transport to and from the operating room. When the patient had recovered normal spontaneous activity and reacted adequately, the gastric tube was removed and the patient discharged to the surgical ward.

Data analysis

The recordings of motility tracings were assessed manually and each phase of IDMC was identified and analysed separately. An IDMC was defined as the motility pattern from the beginning of one phase III to the beginning of the next.

Motility was assessed as follows. For phase I, the duration was noted. Phase II was assessed for its duration and for frequency and amplitude of contraction, and a motility index (frequency × amplitude) was calculated: each phase II was divided into 5-min intervals for which frequency and average amplitude were calculated for each recording site. Phase III of the IDMC was defined as a co-ordinated burst of activity propagating caudad. Each phase III was assessed for its duration, frequency of contraction (min^{-1}), amplitude and velocity of propagation (cm min^{-1})

at each recording site. "Incomplete phase III", defined as phase III occurring with only antral *or* duodenal components, was also noted.

The median of the highest and lowest pH was calculated for each 5-min epoch.

The motility data for each phase of the IDMC at each recording site and the pH before, during and after operation were pooled and compared. The analysis of motility and pH was excluded in one patient because of displacement of the gastric tube during anaesthesia.

Serum paracetamol concentrations were measured by high pressure liquid chromatography [13]. Paracetamol absorption was assessed from the serum concentrations at each sampling time, the peak paracetamol concentrations (*C*max), the time to reach the peak (*t*max) and the area under the serum concentration curve (AUC).

Statistical analysis

Statistical analysis was carried out with the Mann–Whitney *U* test, the Kruskall–Wallis test, the Fisher's exact test and the Spearman rank correlation coefficient, $P < 0.05$ being considered significant. Values are given as medians with quartile spans, range, or both.

RESULTS

Fifty-five IDMC (from three to seven in each patient) were observed during the recording periods. The pre-, per- and postoperative recording times were a median of 40 min (16–265 min), 210 min (105–385 min) and 180 min (70–265 min), respectively. A correlation between the duration of anaesthesia and the time of recovery was found (Spearman's Rho = 0.727; $P < 0.02$) (fig. 1).

None of the patients had abnormal patterns of motility before anaesthesia. Eighty percent of the phase II observed had episodes of antral contractions. Ten phase III (one or two in six patients) were seen and 50% of these had an antral component. pH profiles were narrow: the medians of the lowest and highest values were 1.7 (1.0–2.2) and 2.0 (1.2–2.6).

The pre-, per- and postoperative durations of the IDMC and the durations of phases I, II and III are presented in table I.

An example of the motility tracings is shown in figure 2.

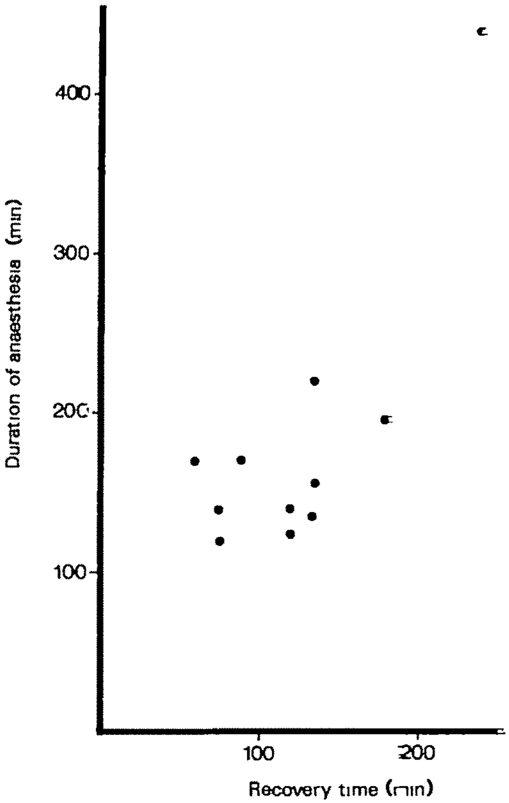

FIG. 1. Correlation between the duration of anaesthesia and recovery time.

Antroduodenal motility and pH during anaesthesia

Anaesthesia was induced during phase II in all patients. The induction dose of pethidine (0.63 mg kg^{-1} (0.57–0.88)) initiated, after a median of 2 min 48 s (1–4 min), a burst of propagating

TABLE I. *Duration of the interdigestive motility complex (IDMC), phase I, II and III in the pre-, per- and postoperative periods (medians with quartile spans). Kruskall–Wallis test:* *P < *0.01*

	Before op.	During op.	After op.
IDMC (min)	106.5 (90–155)	30* (5–56)	32* (18–42)
Phase I (min)	29 (20–56)	14 (2–27)	14 (3–27)
Phase II (min)	45 (22–73)	8* (0–20)	20* (2–43)
Phase III (min, s)	6, 8 (4, 11–8, 34)	6, 27 (4, 33–10, 35)	4, 56 (2, 4–6, 36

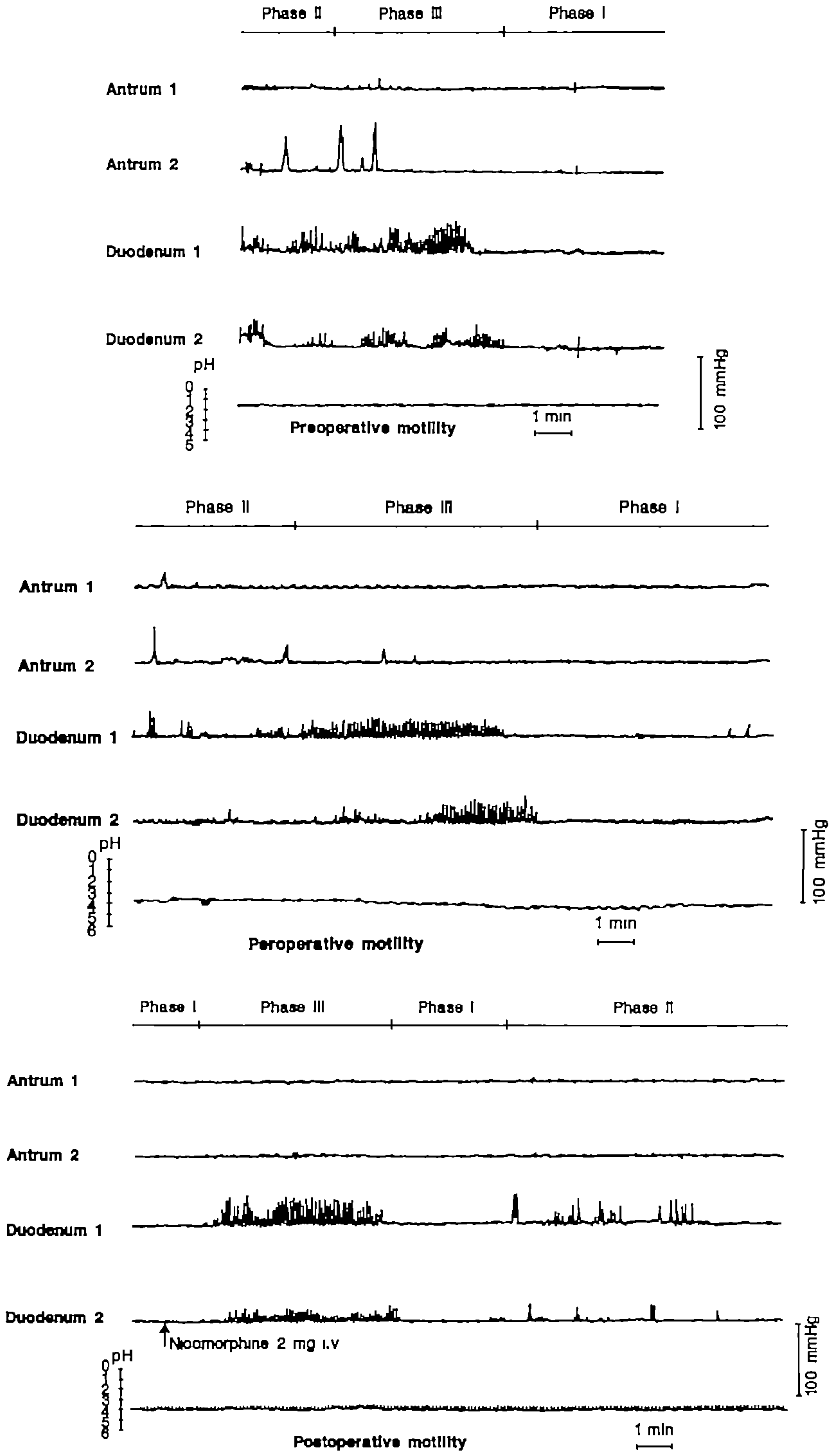

FIG. 2. Antroduodenal pressure activity in the pre-, per- and postoperative periods.

activity resembling phase III of the IDMC. In three patients there was an antral component, and in eight patients only duodenal contractions. Thiopentone (median dose 6.38 mg kg^{-1} (4.5–8.7)) was given during the provoked phase III and did not alter the pattern of motility.

Following the administration of 0.1–2.0% halothane, no connection was found between injections of maintenance doses of pethidine (median 0.37 mg kg^{-1} h^{-1} (0.21–0.42)) and the occurrence of phase III. Although the duration of the cycle varied considerably within and between subjects, the durations of the IDMC were considerably reduced ($P < 0.001$), mainly as a result of a reduced duration of phase II ($P < 0.01$) (table I), which correlated with the inhaled concentrations of halothane (Spearman's Rho $= -0.721$; $P < 0.01$) (fig. 3).

Anaesthesia impeded antral motility during phase II; only 20% of the observed phase II had episodes of antral contractions ($P < 0.01$). The frequency of contractions did not change with anaesthesia, but the amplitudes diminished ($P < 0.01$). The duodenal phase II recordings showed an unchanged frequency of contractions, with increased amplitudes in the pyloric part and diminished amplitudes in the distal part ($P < 0.01$) (figs 4, 5). In spite of this, the motility index was unchanged in the antrum, and increased in the duodenum ($P < 0.05$).

Thirty-eight phase III (from three to seven in each patient) were seen during anaesthesia. Thirty-four percent had an antral component, with an unchanged frequency of contractions, but diminished amplitudes ($P < 0.01$). The duodenal recordings showed a discrete but significant decrease in frequency ($P < 0.05$), while the amplitudes and the propagation were unchanged (tables II–IV).

Anaesthesia gradually reduced the acidity of the

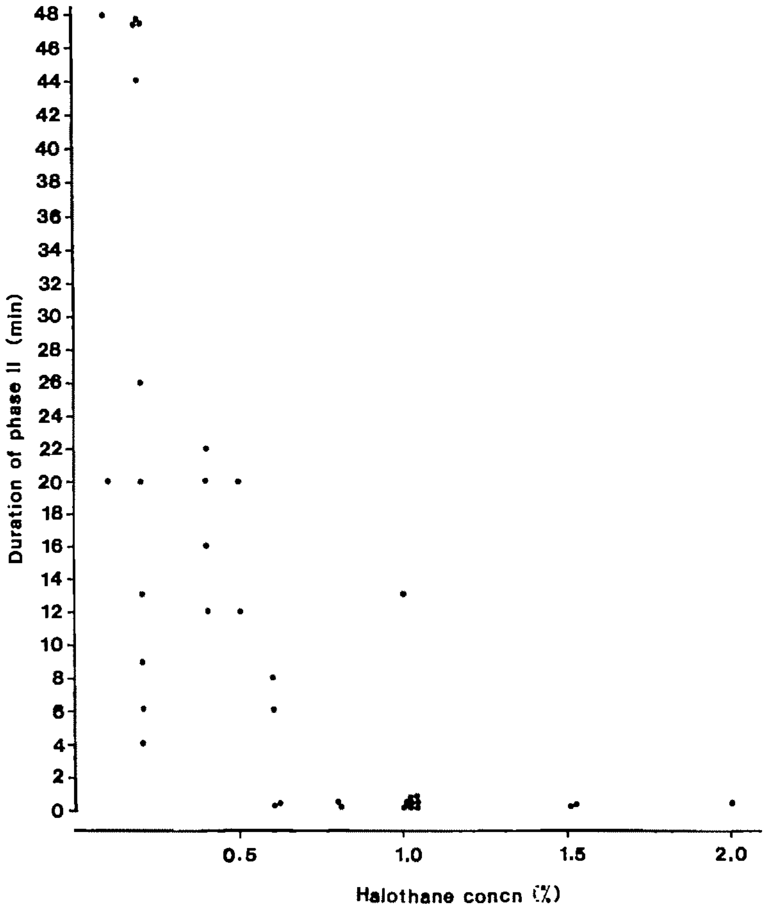

FIG. 3. Correlation between inhaled concentrations of halothane and duration of phase II.

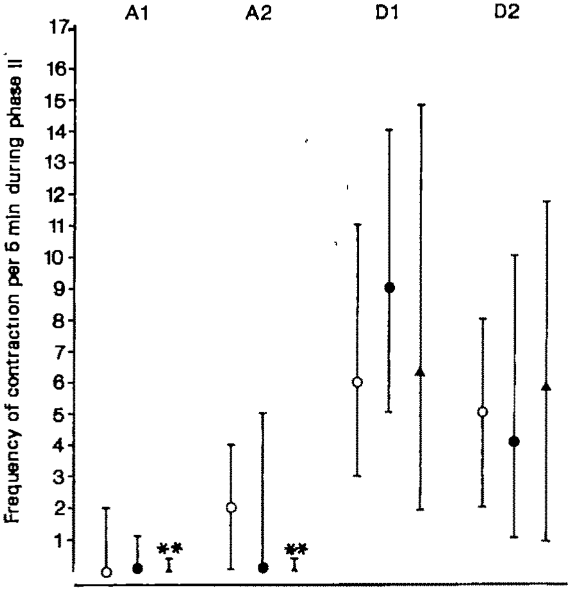

FIG. 4. Frequency of contractions per 5 min during phase II in the pre- (○), per- (●) and postoperative (▲) periods (medians with quartile spans). Kruskall–Wallis test: $^{**}P < 0.01$.

TABLE II. *Frequency of contractions (min^{-1}) during phase III (medians with quartile spans). Kruskall–Wallis test:* $^{*}P < 0.01$

	Before op.	During op.	After op.
Antrum 1	0.1 (0–3)	0.1 (0–3)	0
Antrum 2	0.2 (0–3)	0.1 (0–3)	0
Duodenum 1	10.8 (9.8–11.3)	9.7* (8.7–10.4)	9.0* (8.6–10.0)
Duodenum 2	11.7 (11.0–12.2)	10.1* (9.8–10.8)	10.7* (9.9–11.3)

TABLE III. *Amplitudes of contraction (mm Hg) during phase III (medians with quartile spans). Mann–Whitney and Kruskall–Wallis test:* $^{*}P < 0.01$

	Before op.	During op.	After op.
Antrum 1	34.0 (16–84)	12.5* (10–15)	—
Antrum 2	29.5 (20–42)	15.8* (14–34)	—
Duodenum 1	27.0 (14–30)	30.0 (23–36)	31.0 (21–41)
Duodenum 2	27.0 (22–32)	25.0 (14–31)	24 (20–31)

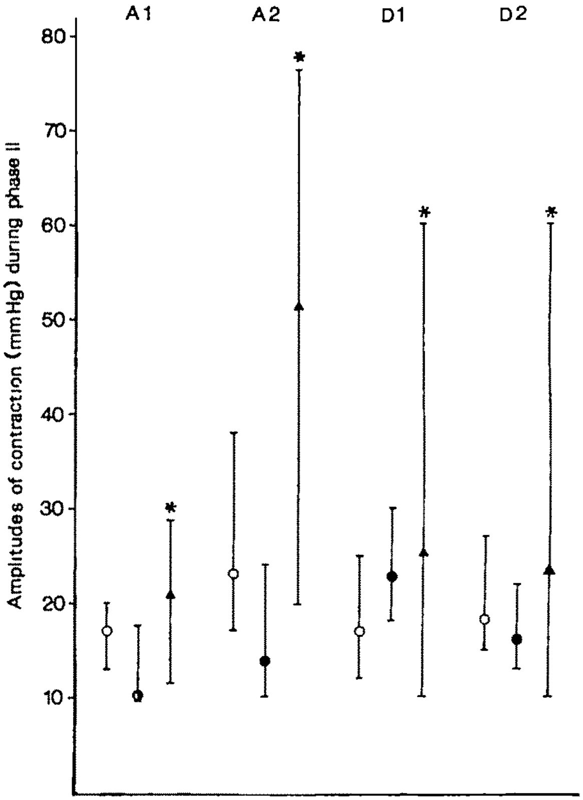

FIG. 5. Amplitudes of contraction (mm Hg) in the pre- (○), per- (●) and postoperative (▲) periods (medians with quartile spans). Kruskall–Wallis test: $^{*}P < 0.05$.

stomach contents: the medians of the lowest and highest pH values were 3.6 (2.4–5.5) and 4.5 (2.8–6.0) during phase II and 2.9 (2.3–5.0) and 3.7 (2.7–5.8) during phase III ($P < 0.01$).

The injection of neostigmine plus atropine at the end of surgery did not alter the current pattern of motility.

Antroduodenal motility and pH during the recovery period

Four patients received analgesia (nicomorphine in doses of 2 mg i.v.) in the postoperative period. Injection of the opioid provoked bursts of activity resembling phase III.

The reduction in the duration of phase II continued in the postoperative period and antral phase II activity seemed more restrained than during anaesthesia. Only a few episodes of antral activity were seen, and showed a decline in the frequency of contractions ($P < 0.01$); frequencies in the duodenal tracings were unchanged

TABLE IV. *Velocity of propagation (cm min^{-1}) of the contraction wave during phase III (medians with range). Mann–Whitney and Kruskall–Wallis test: no significant differences*

	Before op.	During op.	After op.
Antrum 1	—	—	—
Antrum 2	15.1 (6.3–30.0)	9.4 (3.2–29.0)	—
Duodenum 1	9.2 (2.6–19.2)	7.9 (2.0–30.0)	8 9 (5.1–38.9)
Duodenum 2	5.7 (2.4–24.0)	4.3 (1.8–21.8)	5.4 (1.5–48 0)

compared with pre- and peroperative findings, but the amplitudes of contractions increased at each recording site ($P < 0.01$).

Twenty-eight phase III (from one to seven in each patient) were observed, all incomplete, with missing antral contractions. The postoperative duodenal phase III recordings did not differ from the recordings during anaesthesia (reduced frequency, unchanged amplitudes and propagation) (tables II–IV).

The increase in gastric pH persisted into the recovery period ($P < 0.01$); medians of lowest and highest values were 4.0 (2.5–5.0) and 4.4 (2.8–5.4) during phase II and 4.9 (1.8–5.8) and 5.1 (2.1–6.1) during phase III.

Gastric emptying

Eight patients showed a slow rate of gastric emptying during anaesthesia. They achieved *C*max (paracetamol) of 4.1 µg ml^{-1} (0.9–8.9 µg ml^{-1}) in the recovery period; *t*max was 5.5 h (fig. 6). The motility in these patients (seven tracings) was characterized by missing or shortened phase II (0–20 min). Eight phase II were registered and none had episodes of antral contractions. The phase III were incomplete.

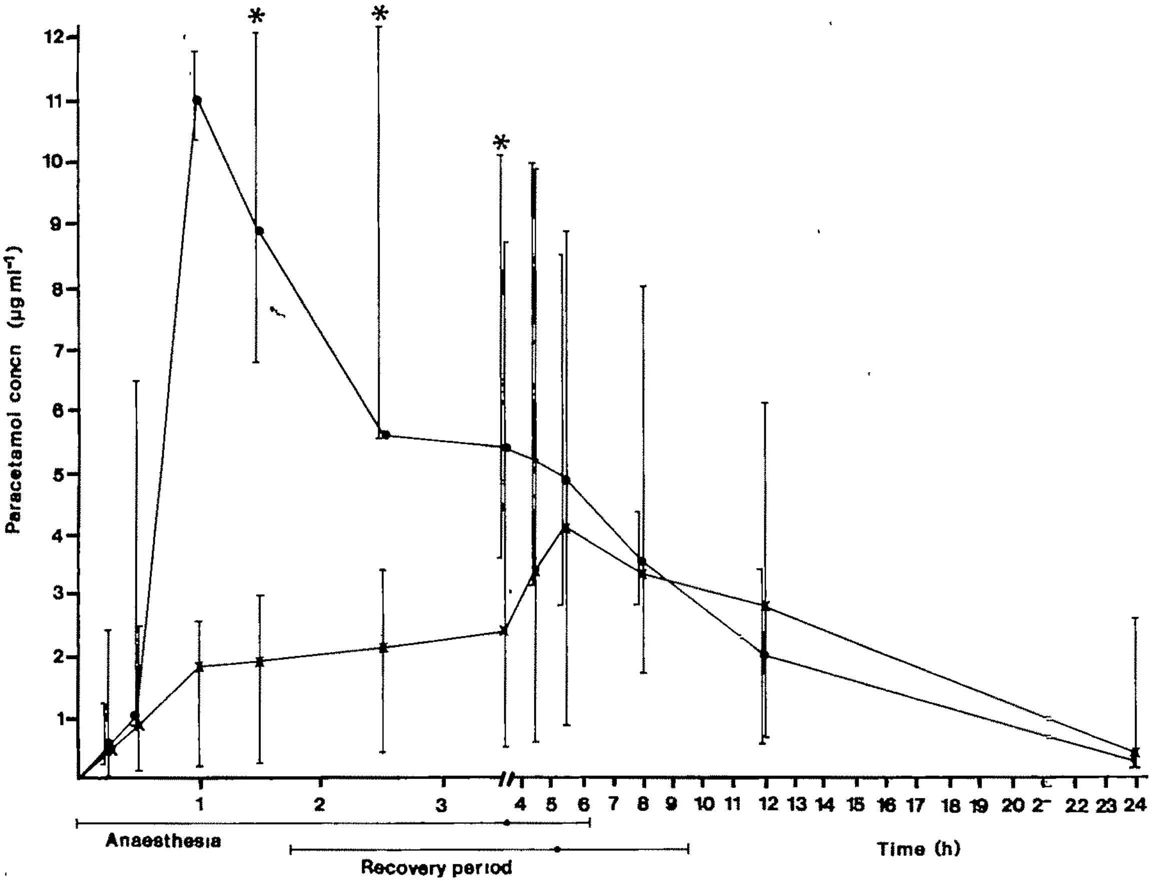

FIG. 6. Paracetamol absorption curves for patients having *C*max during anaesthesia (●) ($n = 3$) and for patients having delayed gastric emptying (x) ($n = 8$). *Significant difference in duration of phase II ($P < 0.05$).

Three patients had peak concentrations of paracetamol during anaesthesia. *C*max (11.0 µg ml^{-1} (10.4–11.8)) was reached 60 min after ingestion (fig. 6). The duration of phase II in these patients was less reduced (20–65 min) ($P < 0.05$). Ten phase II were seen and seven had episodes of antral contractions. The phase III were all complete, with antral contractions.

DISCUSSION

Many factors may influence gastroduodenal motility and gastric emptying during anaesthesia and surgery, including drugs given and the hormonal response. Usually, several drugs are given in association with general anaesthesia and the effects of most of them on gastroduodenal motility, gastric pH and rate of gastric emptying are not known. We investigated the effects of a standard general anaesthesia with halothane and found it to impede motility in the gastric antrum during phase II, decrease the amplitudes of antral contractions during phase III and delay gastric emptying rate. Gastric acid secretion was reduced.

Diazepam is commonly administered by mouth as premedication. It reduces the acidity of stomach contents, increases the amplitudes of contraction and may tend to increase gastric emptying rate [14, 15].

Paracetamol has only minor influence on the variables studied (unpublished observations). It was given to our patients, with a small volume of water, before induction of anaesthesia. $T_{\frac{1}{2}}$ for the rate of emptying of 400 ml of saline solution is known to be 17 min and the risk of pulmonary aspiration was considered to be small [16].

No change in motility was seen at the time of injection of thiopentone. Thiopentone itself is associated with a shortlasting stimulation of mechanical activity in the duodenum in animals [6, 7, 17]. This effect could not be reproduced, probably because thiopentone was given during the opioid-provoked phase III. Because of the short duration of effect, thiopentone was not considered responsible for changes found.

It was not possible in this study to evaluate the effects of pancuronium on gastrointestinal motility. No changes were seen in relation to its administration, although both adrenaline and, especially, noradrenaline concentrations have been found to be augmented by injection of pancuronium during anaesthesia with halothane [18]. Dopaminergic agents are probably involved in gastric relaxation [19].

Injection of the mixture of atropine and neostigmine did not affect the pattern of motility. This may be explained by the ability of neostigmine to counteract the effect of atropine: atropine is known to reduce gastric motility and induce gastric relaxation, while neostigmine enhances gastric contractions [20].

Some of the changes in antroduodenal motility might have been influenced by the perioperative administration of opioid drugs which are known to inhibit the motility in gastric antrum and induce bursts of small intestinal activity [21]. In spite of this, the frequency of contractions did not diminish and the occurrence of phase III activity did not correlate with the injections during anaesthesia. This might be explained by the ability of halothane to antagonize the effects of opioids [8].

Preliminary studies have shown a close relation between phase II motility and the rate of gastric emptying, and that 82% of normal healthy subjects reach peak concentrations of paracetamol within 90 min [22]. Gastric emptying rate was delayed in 73% of the patients investigated here, and this study seems to confirm the association between the occurrence of antral phase II activity and gastric emptying rate.

Control of gastrointestinal motility is exerted at various levels from smooth muscle cell to the brain. This stratification of control includes both neural and humoral mechanisms. Hormones participate in the control of gastrointestinal motility, but their role is not well defined [5], except for that of motilin, which shows a peak concentration in the normal state before phase III [23]. Halothane depresses the sympathetic nervous system and vagal tone [24, 25]. The effects of general anaesthesia with halothane on antroduodenal motility might be explained by these effects. The increased amplitudes and the decreased frequency in the antrum in the recovery period might be caused by the increase in plasma catecholamines which follows anaesthesia with halothane [19, 26]. The depression of vagal tone is probably responsible for the increase in gastric pH, as vagal tone is the prime regulator of gastric acid secretion.

It is difficult to predict the clinical importance of the results in this investigation. The risk from inhalation of acid gastric contents seems to be reduced during and after the anaesthetic procedure we used, as gastric acid secretion is reduced, but this may be counteracted by the possible increase in risk of aspiration of hypertonic gastric fluids as a result of the delay in gastric emptying.

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COMPARISON OF 1.5% ENFLURANE WITH 1.25% ISOFLURANE IN OXYGEN FOR CAESAREAN SECTION: AVOIDANCE OF AWARENESS WITHOUT NITROUS OXIDE

M. E. TUNSTALL AND A. SHEIKH

SUMMARY

We examined the feasibility of administering nearly 100% oxygen throughout the induction–delivery period of general anaesthesia for 113 Caesarean sections. Isoflurane 1.25% was compared with 1.5% enflurane for maintenance of anaesthesia. The level of anaesthesia was monitored by use of the isolated forearm technique. There was a greater amount of isolated forearm movement when enflurane was used. The three main criteria for a satisfactory general anaesthetic technique for Caesarean section were fulfilled, namely no maternal awareness, no undue depression of the fetus and no adverse effect on uterine contractility. Isoflurane and enflurane appear to be suitable anaesthetic agents for facilitating hyperoxygenation during Caesarean section.

In clinical practice situations abound in which fetal oxygen supply is compromised. Thus maternal hyperoxygenation may be a reasonable interim measure before Caesarean section and equally reasonable during Caesarean section [1].

A maternal fractional concentration of inspired oxygen ($F_{I_{O_2}}$) of 1.0 results in the greatest concentrations of oxygen in cord blood at delivery by section, during both general and extradural anaesthesia. In the former, umbilical venous oxygen tensions of 4.0, 4.7 and 5.5 kPa, corresponding to maternal $F_{I_{O_2}}$ values of 0.3, 0.66 and 0.95, have been reported [2]. In the latter, umbilical vein oxygen tension values of 3.7, 4.8, 5.5 and 6.3 kPa, corresponding to maternal $F_{I_{O_2}}$ values of 0.21, 0.47, 0.74 and 1.0, have been reported [3]. However, no significant improvement in the Apgar scores in the latter series could be related to increased maternal inspired oxygen concentrations. In general anaesthesia it would be useful to establish a reliable technique in which it was possible to administer almost 100% oxygen to the mother from induction to delivery. The technique should fulfil three criteria: no maternal awareness; no undue depression of the fetus; no significant effect on uterine contractility.

Isoflurane and enflurane are satisfactory agents for general anaesthesia in Caesarean section. In combination with 50% nitrous oxide, 0.5% and 1% enflurane [4, 5] and 0.75% isoflurane [5] have been shown to meet the three criteria specified. If nitrous oxide is withdrawn in order to permit higher maternal inspired oxygen concentrations, a proportionate increase in the amount of volatile agent is needed to maintain anaesthesia. Both enflurane and isoflurane are potent analgesic agents and their uptake and excretion is relatively rapid, as both have low blood:gas partition coefficients. Provided they are not administered in excess of 1.5 MAC, there is no important effect on uterine contractility [6]. The intermittent inhalation of 1% enflurane [7], or 0.75% isoflurane [8] for the relief of pain in labour have been shown to be more effective than 50% nitrous oxide. However, both the volatile agents produce more drowsiness than does nitrous oxide.

Preliminary observations were made during Caesarean sections under general anaesthesia, on the effects of withdrawing nitrous oxide and replacing it with an increased inspired concentration of either enflurane or isoflurane. Depth of anaesthesia was monitored using the isolated forearm technique [9]. Either 1.5% enflurane or

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1.25% isoflurane in oxygen only, was found to be acceptable as sole maintenance agent. It was then decided to make a more formal comparison of the use of the two agents in a study approved by the Joint Ethics Committee of the Grampian Health Board and University of Aberdeen.

PATIENTS AND METHODS

A consecutive series of mothers for elective and semi-elective Caesarean section under general anaesthesia were allocated randomly to receive either enflurane or isoflurane. Patients in whom the fetus was at risk because of factors such as prematurity, intra-uterine growth retardation or pre-eclamptic toxaemia were included, as it is the at-risk fetus which is most likely to benefit from maternal hyperoxygenation. According to established custom, all mothers were told that they would be spoken to during anaesthesia. Any explanation required by the mother was given in detail and the purpose of a pneumatic tourniquet on the right arm was stated. Unless there were contraindications, the mother walked from the ward to the operating theatre, accompanied by a nurse. Whenever possible, the mother examined the operating theatre on the evening before the operation.

A standard pre-anaesthetic procedure, including H_2-antagonists, sodium citrate, lateral tilt, pre-oxygenation and cricoid pressure was used. Immediately before induction of anaesthesia, the pneumatic tourniquet was automatically inflated on the restricted right arm. Anaesthesia was induced with thiopentone 250 mg i.v., followed by suxamethonium 100 mg i.v.; the trachea was intubated and the lungs ventilated mechanically with 100% oxygen. Placement of a catheter was performed after the patient was anaesthetized.

Two minutes after the start of the thiopentone injection (which was taken as time zero) the anaesthetic vaporizer was turned to the 3% setting. At the same time the mother was asked to grip and release the anaesthetist's hand with the hand of her isolated forearm. The request was repeated at 1-min intervals, or as required until delivery. A positive response indicated wakefulness and a mark was entered in the first column on a record form. At the same intervals of time, the amount of spontaneous movement of the hand (0; + = some movement; ++ = sustained movement or posture; +++ = very vigorous movements) was entered in a second column. (These classifications were subsequently scored 0, 1, 2 and 3, respectively.) If the anaesthetist's hand was gripped without being released on the command to open and shut the hand, it was classified as reflex grip and a mark was entered in a third column.

After 3 min of delivering either enflurane or isoflurane at 3% concentration, the vaporizer was adjusted to deliver 1.5% enflurane or 1.25% isoflurane. The lungs were ventilated using a Blease–Manley ventilator with a fresh gas flow of oxygen 7–8 litre min^{-1} and the flow was adjusted to maintain an end-tidal carbon dioxide partial pressure of 3.6–4.4 kPa. The last reading observed and recorded before delivery was assumed to apply to the time just before delivery. Neuromuscular blockade was maintained with atracurium 25–30 mg.

Following delivery, oxytocin 10 units was given i.v., 66% nitrous oxide was introduced and the vaporizer setting adjusted down 0.5%. Metoclopramide 10 mg and papaveretum 20 mg were given i.v. Two-millilitre samples of cord arterial and venous blood were taken for analysis.

RESULTS

The records of 113 consecutive patients were analysed. Twenty-five were primiparous. Fifty received enflurane and 63 isoflurane. The age, height, weight and parity distributions were similar in both groups. There were only 24 clinically acceptable "A" patients as defined by Crawford [10], nine of whom received enflurane and 15 isoflurane. Blood loss was unremarkable in all patients and none required fluid replacement.

No mother experienced awareness (that is, postoperative recall) and no mother experienced dreams. Wakefulness was observed in 24 patients who received enflurane and in 23 who received isoflurane at the 2-min interval. The overall frequency of wakefulness 2 min after commencing the injection of thiopentone was therefore 42% for the whole series. At the 3-min interval, four patients receiving isoflurane and eight who received enflurane remained wakeful; at 4 min only two patients were wakeful (both receiving enflurane). At the 5-min interval (that is, after the inhalation of volatile agent for 3 min) no mother was wakeful. There was 100% amnesia for episodes of "wakefulness".

For the 2–5 min intervals inclusive, 14 patients

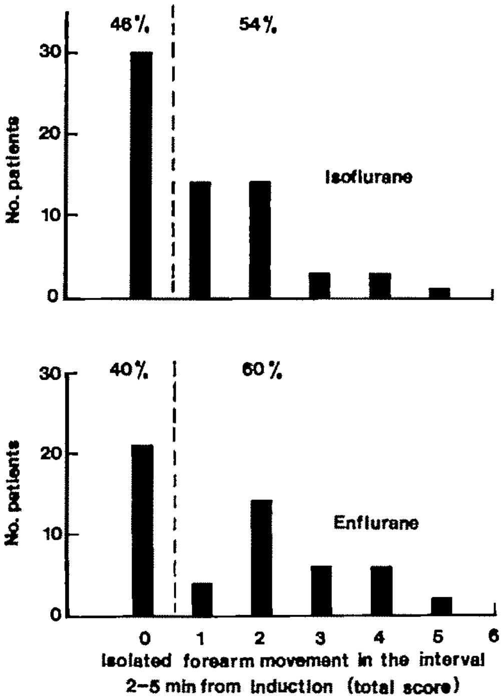

FIG. 1. Totals of movement scores for the isolated forearm recorded at 2, 3, 4 and 5 min from the commencement of i.v. induction of anaesthesia. The dotted line separates the patients with no movements (score 0) from the rest, and the percentages are shown.

in the enflurane group and seven patients in the isoflurane group had total movement scores of 3 or more (fig. 1). For the intervals from 5 min to delivery, 51 % of patients in the isoflurane group, but only 6 % of patients receiving enflurane, produced no arm movements and were therefore in "surgical anaesthesia" (fig. 2). Because mothers wakeful at 2 min (before the introduction of the volatile agent) might be considered relatively resistant to anaesthesia, their scores after 5 min were considered separately, and are shown in figure 3. None of the patients in this category who had received enflurane became "surgically anaesthetized" before delivery. The mean weight of the mothers who were wakeful in the first few minutes was 76.3 kg, compared with 73.0 kg in those not wakeful ($P > 0.05$).

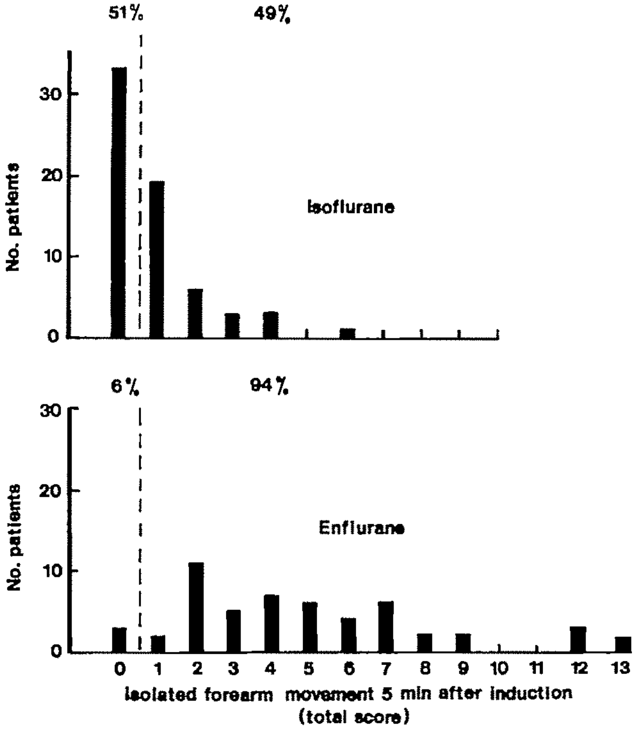

FIG. 2. Totals of movement scores for the isolated forearm recorded at 1-min intervals at and from 6 min to delivery. The dotted line separates the patients with no movements (score 0) from the rest, and the percentages are shown.

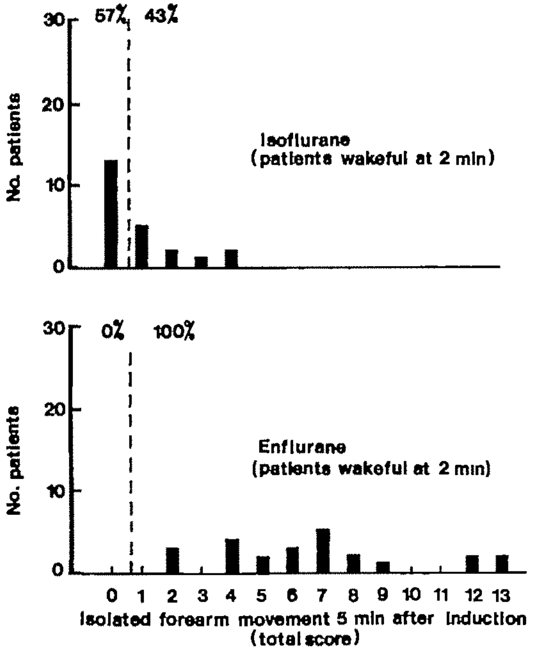

FIG. 3. Totals of movement scores for the isolated forearm recorded at 1-min intervals at and from 6 min to delivery; only in mothers wakeful at 2 min. The dotted line separates the patients with no movements (score 0) from the rest, and the percentages are shown.

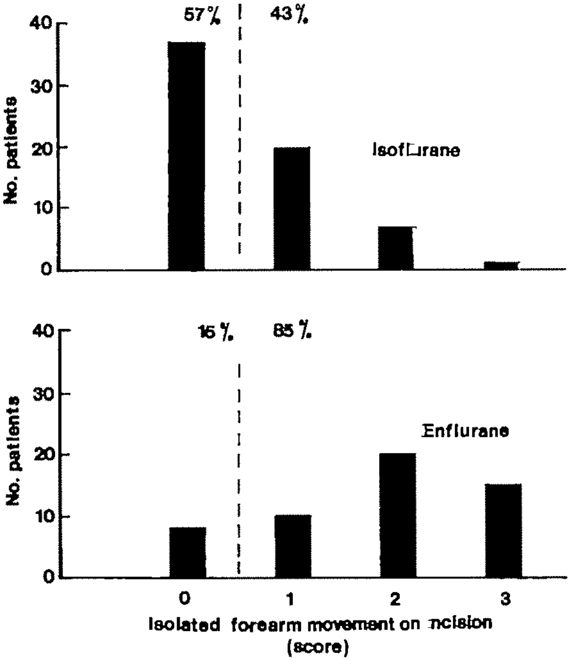

FIG. 4. Movement scores at the time of the skin incision. The dotted line separates the patients with no movements (score 0) from the rest and the percentages are shown. Score 1 = some movement; 2 = sustained movement or posture; 3 = very vigorous movements.

Induction–incision intervals in both groups were similar. The mean values were 9.2 min for enflurane and 8.7 min for isoflurane. Hand movements on incision were more active in the enflurane group (fig. 4).

Reflex grip, as described earlier, represents the level of anaesthesia just short of wakefulness and was recorded at 2 min in eight patients in the enflurane group and nine patients who received isoflurane and at 3 min in one enflurane patient. In the period from 6 min to delivery, reflex grip occurred in 18 patients in the enflurane group and one who received isoflurane. The mean induction–delivery interval for both groups was 16 min. In the period from 6 min to delivery, wakefulness occurred in only one subject (who received enflurane) at 12 min, the time of delivery.

The distribution of Apgar minus colour (A–C) scores of 8, 7, 6, 5, 4, 3, 2 and 1 at 1 min were, respectively, for isoflurane: 45, 7, 2, 3, 4, 0, 0 and 2 babies, and for enflurane: 36, 6, 4, 0, 3, 0, 1 and 0 babies. At 5 min the scores were, for isoflurane: 58, 3, 1, 0, 0, 0, 1 and 0 babies, and for enflurane: 44, 4, 1, 0, 0, 0, 1 and 0 babies. Two babies with low scores underwent tracheal intubation for elective mechanical ventilation: one at 31 weeks gestation on account of prolonged rupture of the membranes with infection, and one at 32 weeks gestation for intra-uterine growth retardation, increasing Rhesus antibody titre and stillbirth of a previous sibling. Both babies made good progress. There were only two babies with less than perfect Apgar scores at 1 min which could not be accounted for by obstetric pathology, except that in one mother the left lateral tilt may not have relieved aorto–caval compression sufficiently. Both babies had A–C scores of 8 at 5 min; both mothers had received isoflurane.

Because of their relevance to the results of the cord blood samples, the last recorded maternal end-tidal carbon dioxide partial pressure before delivery in each group was compared (table I). Greater mean carbon dioxide tensions and lower pH values were present in umbilical vein blood of

TABLE I. *Maternal end-tidal carbon dioxide partial pressure (kPa) shortly before delivery*

	Enflurane ($n = 49$)	Isoflurane ($n = 56$)
Mean (SEM)	4 0 (0.05)	3.8 (0.04)
Range	2.9–4.8	3.3–4 7

TABLE II. *Umbilical vein blood at delivery (mean values (SEM)*

	Enflurane ($n = 50$)	Isoflurane ($n = 63$)
pH	7.319 (0 0057)	7.337 (0.0046)
$P\mathrm{CO}_2$ (kPa)	5.75 (0.073)	5.55 (0.065)
$P\mathrm{O}_2$ (kPa)	5.15 (0.219)	5 14 (0.220)

TABLE III. *Umbilical artery blood at delivery (mean values (SEM))*

	Enflurane ($n = 50$)	Isoflurane ($n = 63$)
pH	7.273 (0.0050)	7.284 (0.0043)
$P\mathrm{CO}_2$ (kPa)	7.11 (0.088)	6.96 (0.081)
$P\mathrm{O}_2$ (kPa)	2.47 (0.094)	2.46 (0.103)

the enflurane group (table II). The blood-gas tensions for the umbilical artery are shown in table III. The three highest cord blood oxygen tensions achieved in umbilical vein were 8.1, 11.1 and 12 kPa, and the highest value achieved in any umbilical artery sample was 4.7 kPa.

DISCUSSION

If it is assumed that the MAC values of isoflurane and enflurane are 1.3 and 1.7 respectively, that the uptake pattern of both agents is the same, and that the ratio of the inspired to the alveolar fraction is approximately 0.6 during the latter half of the induction–delivery interval, it follows that the concentrations of isoflurane and enflurane used were not equipotent. To correspond with a vaporizer concentration of 1.25% isoflurane, we should have used 1.63% enflurane, not 1.5%. However, 1.5% enflurane is easier to select from the calibration markings on the controls of the vaporizer. Furthermore, in preliminary investigations, no episode of wakefulness had developed after the first 5 min in any patient who had received 1.5% enflurane.

This study suggests that the 3%–1.25% sequence for isoflurane may be used without the isolated forearm technique of monitoring to prevent awareness. In view of the marked isolated forearm activity with 1.5% enflurane, an increased dose with a 3%–1.75% sequence should, perhaps, be used in future. The advantage of using the isolated forearm technique on a regular basis is that, if wakefulness is treated in time, there will be no awareness.

In general, the use of high oxygen concentrations has not been shown to confer any special advantage in obstetric anaesthesia where the baby is not compromised. Therefore, unless one is monitoring for wakefulness, the addition of 50% nitrous oxide to the inhaled gases gives assurance that at least 0.45 MAC of anaesthetic value is being administered.

An anaesthetic technique containing 50% nitrous oxide with 0.5% halothane, 0.75% isoflurane or 1% enflurane does not require monitoring with the isolated forearm technique. It would be exceptional for any mother to suffer awareness with these regimens.

The avoidance of nitrous oxide in general anaesthesia for Caesarean section allows hyperoxygenation. This does not prevent the anaesthetist meeting the three criteria of no awareness, no undue fetal depression, and no significant uterine relaxation. This study shows that it is possible to give a satisfactory general anaesthetic for Caesarean section without nitrous oxide, using one of the two newer volatile agents, isoflurane or enflurane, in oxygen.

Any advantage to the fetus of maternal hyperoxygenation may be lost if perfusion of the intervillous space is not maintained [11]. This depends on avoidance of aorto–caval compression, maintenance of adequate maternal arterial pressure, and avoidance of factors which provoke uterine artery vasoconstriction.

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PRELIMINARY EVALUATION OF THE ENCLOSED MAGILL BREATHING SYSTEM

W. E. BRUCE AND N. C. SONI

SUMMARY

The Enclosed Magill anaesthetic breathing system may be used for both spontaneous ventilation and controlled ventilation with similar fresh gas flows. During spontaneous ventilation, a fresh gas flow between estimated alveolar ventilation and minute ventilation is adequate and the system performs as a Mapleson A type breathing system. For controlled ventilation, a fresh gas flow of 70–100 ml kg^{-1} min^{-1} produces normocapnia in most subjects, as demonstrated in this limited study. These values are similar to those demonstrated for type D breathing systems. It is suggested from this preliminary study that the breathing system conforms to the requirements of a universal breathing system in as much as similar fresh gas flows are used in both modes of ventilation.

The Enclosed Magill Anaesthetic Breathing System devised by Voss [1] is an interesting modification of a Mapleson A breathing system. In this new configuration the fresh gas flow required for normocapnia to be maintained is similar in both spontaneous and controlled ventilation modes; in this respect the breathing system may be described as a universal breathing system.

The purpose of this study was to evaluate the function of the Enclosed Magill Breathing System during both spontaneous and controlled ventilation.

THE BREATHING SYSTEM

The Enclosed Magill Breathing System, Enclosed Afferent Reservoir (EAR) [2] consists of a modified Mapleson A Breathing System (fig. 1). The fresh gas flow passes into a bag, the enclosed reservoir, on the inspiratory limb of the system. This bag is mounted within a rigid bottle. The expiratory limb of the system leads back to the bottle and there is a one-way valve proximal to the entrance of the expiratory limb to the bottle. The expiratory limb is continuous with the bottle and has a Heidbrink valve and rebreathing bag, open reservoir, placed distally.

During spontaneous ventilation, the patient inspires from the enclosed reservoir bag on the inspiratory limb, and is prevented from breathing gas from the expiratory limb by the closure of the one-way valve.

On expiration, the one-way valve opens, allowing spillage of the expired gas. Fresh gas flowing into the inspiratory limb and filling the enclosed reservoir limits expiration into the inspiratory limb, but the majority of the early expiratory gas, potentially able to reflux into the inspiratory limb, should be deadspace gas. In this respect the system should perform as a Mapleson A with the expiratory valve distal from the patient. This is similar to the configuration of either the Lack or ADE systems.

Controlled ventilation with this system can be undertaken either with a ventilator or manually by squeezing the bag placed at the end of the distal part of the expiratory limb. Expired gases spill through either the ventilator or the Heidbrink valve.

On inspiration, pressure exerted at the distal end of the expiratory limb closes the one-way valve and increases the pressure in the bottle, thereby squeezing the enclosed reservoir bag. This forces fresh gas into the patient. On expiration, expired gas passes into both limbs of

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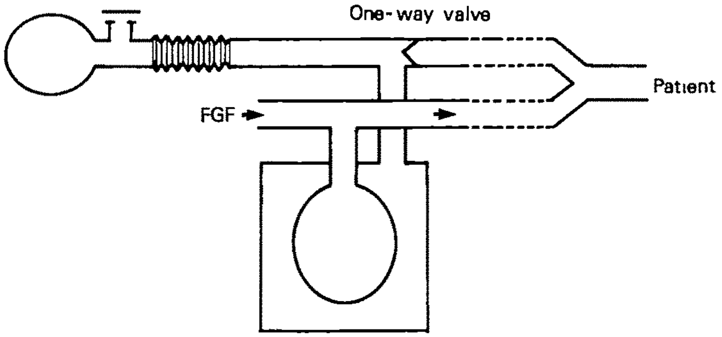

FIG. 1. The Enclosed Magill breathing system.

the system. Fresh gas influx limits the passage of expired gas into the inspiratory limb, tending to conserve fresh gas from the deadspace. The one-way valve opens and expired alveolar gas is vented into the expiratory limb and out through either the ventilator or the Heidbrink valve, depending on the mode of controlled ventilation. The initial expired gas, from the deadspace, is conserved, provided the one-way valve remains closed until the enclosed reservoir is filled. This differs fundamentally from a D system with which deadspace gas is wasted.

SUBJECTS AND METHODS

The study, which was approved by the Ethics Committee of the Westminster Hospital, was divided into three parts. In the first two parts the performance of the breathing system was assessed in 10 volunteers and subsequently in 10 anaesthetized patients. In the third party of the study the performance of the system was assessed during controlled ventilation in anaesthetized patients. In each part of the study, measurements of end-tidal carbon dioxide were made using an in-line Hewlett–Packard capnograph. A Wright's electronic spirometer was used to measure minute ventilation. The volume of the measuring apparatus, which was situated between the patient and the breathing system, was 34 ml.

Ten volunteer subjects were allowed to breathe spontaneously with the Enclosed Magill Breathing System, at high fresh gas flows. Each of the volunteers had previous experience of breathing with Mapleson A breathing systems in the laboratory and, in the initial part of the study, a period of up to 1 h was allowed for the subject to relax and settle into a relatively normal breathing pattern. During this study a tested Heidbrink valve was attached to the distal segment of the expiratory limb in a fully opened position.

When the subject had settled into a regular and comfortable breathing pattern, fresh gas flow was reduced in increments of 10 ml kg^{-1} min^{-1}, at intervals of 15 min. An attempt was made to prevent the subject from sensing when the fresh gas flow was reduced. In this part of the study, the fresh gas-flow was reduced to the minimum that the volunteer would tolerate.

The second part of the study involved 10 ASA I patients who were undergoing anaesthesia for dental surgery. Each patient received diazepam 10 mg by mouth 2 h before anaesthesia. Anaesthesia was induced with thiopentone 5 mg kg^{-1}, followed by suxamethonium 1 mg kg^{-1}. Topical lignocaine 3 mg kg^{-1} was applied to the larynx, and nasotracheal intubation was performed. Anaesthesia was maintained with the patient spontaneously breathing 1% halothane and nitrous oxide in oxygen. High fresh gas flows were maintained until the breathing pattern stabilized, as seen by no further change in either end-tidal carbon dioxide or minute ventilation over a 10-min period. The fresh gas flow was reduced to 100 ml kg^{-1} min^{-1} and a period of 10 min allowed for stabilization. This was repeated at fresh gas flows of 70 and then 50 ml kg^{-1} min^{-1}.

In the third part of the study, 10 ASA I patients were anaesthetized and studied during controlled ventilation. Each patient received diazepam 10 mg by mouth 2 h before operation. Anaesthesia was induced with thiopentone 5 mg kg^{-1} followed by suxamethonium 1 mg kg^{-1}. Topical lignocaine was applied to the larynx and nasotracheal intubation was performed. Muscle paralysis was maintained using vecuronium 0.1 mg kg^{-1}. The

TABLE I. *Criteria of rebreathing (from [3])*

One or more of the following conditions:

(1) An increase in minute volume or tidal volume of 10% or more, not accompanied by a corresponding decrease in end-expiratory P_{CO_2} ($P_{E'CO_2}$).

(2) An increase in $P_{E'CO_2}$ (or a decrease in $P_{E'O_2}$) of 0.71 kPa or more, which could not be accounted for by a decrease in ventilation.

(3) An increase in ventilation of 5% or more, accompanied by an increase in $P_{E'CO_2}$ of 0.27 kPa or more.

lungs were ventilated with 0.5% halothane and nitrous oxide in oxygen. The minute ventilation was 120 ml kg^{-1} min^{-1} and the tidal volume 10 ml kg^{-1} min^{-1}. A Manley Pulmovent was used. Following a period of stabilization with a fresh gas flow of 70 ml kg^{-1} min^{-1}, a fresh gas flow of 50 ml kg^{-1} min^{-1} was commenced. This was continued over a 10-min period while recordings of end-expired carbon dioxide and inspired carbon dioxide were made. Further recordings were made with fresh gas flows of 70 ml kg^{-1} min^{-1} and 100 ml kg^{-1} min^{-1}, over 10-min periods.

Statistical analysis was by Student's *t* test.

RESULTS

In each of the studies where spontaneous ventilation was assessed, the point of rebreathing in each subject or patient was determined by the criteria of Kain and Nunn [3] (table I). In the volunteer subjects breathing spontaneously, as the fresh gas flow was reduced in increments of 10 ml kg^{-1} min^{-1}, one subject showed evidence of rebreathing at 90 ml min^{-1}. Four volunteers demonstrated evidence of rebreathing at a fresh gas flow of 80 ml kg^{-1} min^{-1} and five volunteers demonstrated rebreathing at a fresh gas flow of 70 ml kg^{-1} min^{-1}. These results can be illustrated in terms of the fresh gas flow to initial minute ventilation ratio, the ratios at which rebreathing occurred being in the range 0.78–1.0 (table II).

Anaesthetized group

One of the anaesthetized patients breathing spontaneously demonstrated evidence of rebreathing at a fresh gas flow of 100 ml kg^{-1} min^{-1}. A further five patients demonstrated rebreathing at 70 ml kg^{-1} min^{-1} and the remaining four patients at 50 ml kg^{-1} min^{-1} (table III).

The differences between volunteers and anaesthetized patients with regard to points of rebreathing, the change in $P_{E'CO_2}$ and the percentage change in minute ventilation were compared statistically. There was a significant difference between the two groups only in the rebreathing points ($P < 0.05$). No difference between the two groups in the increase in end-tidal carbon dioxide or minute ventilation could be demonstrated.

Anaesthetized patients with controlled ventilation

At the standard minute ventilation of 120 ml kg^{-1} min^{-1} with a fresh gas flow of 50 ml kg^{-1} min^{-1}, the mean end-tidal carbon dioxide was 6.55 kPa (range 5.2–7.1 kPa.) At 70 ml kg^{-1} min^{-1} the mean end-tidal carbon dioxide was 5.89 kPa (range 4.7–6.8) and at 100 ml kg^{-1} min^{-1} the mean value was 5.0 kPa (range 4.2–5.8) (table IV).

DISCUSSION

The Enclosed Magill Anaesthetic Breathing System is a modification of the Magill system. During spontaneous ventilation in volunteers, the

TABLE II. *Point of rebreathing in volunteers breathing spontaneously*

Patient	Wt (kg)	FGF (ml kg^{-1} min^{-1})	FGV/$\dot{V}_E$	Change in $P_{E'CO_2}$ (kPa)	Change in minute vent. (%)
1	63	80	0.84	0.71	0
2	95	70	1.0	0	21
3	95	70	0.78	0.67	0
4	76	70	0.9	0	10
5	56	90	0.92	0.27	10
6	80	80	0.8	0.4	11
7	58	80	0.93	0.67	0
8	62	70	0.79	0	10
9	80	70	1.0	0	12
10	65	80	0.84	0	10

TABLE III. *Point of rebreathing in anaesthetized patients breathing spontaneously*

Patient	Wt (kg)	FGF (ml kg^{-1} ml^{-1})	FGV/$\dot{V}\text{E}$	Change in $P\text{E}_{CO_2}$ (kPa)	Change in minute vent. (%)
1	66	50	0.72	0.53	8
2	60	70	0.53	0.4	18
3	60	70	0.75	0.4	6
4	52	70	0.81	0.67	10
5	72	50	0.6	0.27	10
6	69	70	0.65	0.2	11
7	56	100	0.7	0.8	11
8	62	50	0.63	0.4	12
9	52	50	0.56	0.67	12
10	68	70	0.72	0.29	17

TABLE IV. *End-tidal carbon dioxide (kPa) at each fresh gas flow. Minute ventilation set at 120 ml* kg^{-1} min^{-1}

		Fresh gas flow (ml kg^{-1} min^{-1})		
Patient	Wt (kg)	100	70	50
1	59	5.0	5.9	6.5
2	56	4.2	4.7	5.2
3	44	5.8	6.8	7.1
4	47	5.8	6.7	6.8
5	57	4.5	5.0	5.7
6	56	5.0	6.5	6.9
7	57	4.4	5.5	6.8
8	67	5.1	6.1	6.8
9	60	5.0	6.2	6.7
10	46	5.2	5.7	7.0
Mean (SD)		5.0 (0.53)	5.9 (0.69)	6.55 (0.6)

ratio of fresh gas flow to minute ventilation at the point of rebreathing was approximately 0.7:1.0. This is similar to that seen with a Mapleson A type breathing system. Similarly, in the anaesthetized group, rebreathing occurred within a range of fresh gas flows between the values of estimated alveolar ventilation and the basal minute ventilation. This suggests that, in this small study, the Enclosed Magill Breathing System behaves in a manner similar to other A systems and requires a fresh gas flow of greater than estimated alveolar ventilation if rebreathing is to be avoided. We have reported the range of values rather than the mean value, to avoid the suggestion that a mean value is a recommended fresh gas flow [4].

There was a significant difference between the rebreathing points of the volunteers and the anaesthetized patients, but no significant difference regarding change in minute ventilation or increase in $P\text{E}'_{CO_2}$.

There are two aspects of this study which require further comment. The first is that the addition of the measuring apparatus increases the deadspace by 34 ml, and the second relates to the alteration of the dynamics of the breathing system by the apparatus, as it is interposed between the patient and the breathing system. Both factors may influence the results obtained by increasing both the deadspace and the mixing within the system. The functional efficiency of the breathing system may be reduced therefore, so that the breathing system may be more efficient than the results suggest.

When used for controlled ventilation, the system maintains the functional characteristics of an A system, but with an efficiency associated usually with D systems. The conservation of deadspace gas should make the Enclosed Magill more efficient than the D systems in controlled ventilation, as suggested by Voss, and confirmed by Miller and Miller [1, 2].

The results of our study demonstrated a range of values for end-tidal carbon dioxide which varied according to the fresh gas flow. Normocapnia could be maintained with a fresh gas flow of 70–100 ml kg^{-1} min^{-1}, provided the minute ventilation was in excess of this value (120 ml kg^{-1} min^{-1}).

It is of interest that these end-tidal carbon dioxide values differ from the arterial values reported [2] for a similar system. Optimal efficiency of the system depends, as stated by Miller and Miller [2], on the valve remaining closed until the enclosed reservoir fills, thereby conserving deadspace gas. In the prototype used in this study, the valve tended to open prematurely. Voss [1] has suggested that this can be improved by the use of either a flow resistor on the expiratory limb, or a baffle within the Y-piece at the patient connection to divert early expiratory gas towards the enclosed reservoir. Both mechanisms markedly improve efficiency in the controlled mode. The contribution of these mechanisms to the work of breathing in the spontaneous mode has yet to be evaluated. In view of this observation, it is possible that different valves or system construction in the prototypes used may contribute to the variation in results, as may factors such as patient populations or anaesthetic technique.

During controlled ventilation, equilibration was allowed to take place over 10 min. This is grossly inadequate if complete equilibration is to occur [5]. Clinical studies have used a variety of different equilibration periods: 12 min [6], 20 min [7] and 30 min [8]. There is an initial rapid "wash in" or "wash out" change in $P\text{E}'_{CO_2}$ following a change in fresh gas flow. Equilibration with the new fresh gas flow then continues slowly and is not complete for several hours [6, 9]. In this study it was noted that, at the time of measurement, the rate of change in carbon dioxide had decreased to the point of being barely perceptible. Therefore, while accepting that further equilibration would inevitably take place and that carbon dioxide would continue to increase at the lower fresh gas flow rates, for the purposes of this study the value achieved at 10 min may be accepted as representing the end-tidal carbon dioxide value for that fresh gas flow.

There are several practicable features of the breathing system which became apparent during use. While bulky, the system is not obtrusive when the device is mounted on the side of an anaesthetic machine. Testing the system before use, for air-tightness and for valve function, was relatively simple. The enclosed reservoir bag was viewed readily and did not inflate if the one-way valve did not close, while the open reservoir did not inflate if the valve did not open.

The Enclosed Magill has a large volume, and therefore initially a high fresh gas flow is advised to prime the system. During spontaneous ventilation the movement of the bag may be seen clearly through the Perspex bottle and the distal Heidbrink valve is easily accessible. Controlled ventilation is effected with this valve, but compression of the open reservoir bag which in turn compresses the enclosed reservoir bag results in an unusual impression of compliance. The trained hand needs retraining. Switching between the two modes of ventilation requires no more than adjusting the Heidbrink valve. Scavenging is also simple, as the expiratory valve is mounted distal to the patient.

Assembly of the device can be confusing. As with any bag-in-bottle system, there may be leaks, but this can be assessed by pressurizing the system. The one-way valve can become unseated; during controlled ventilation this is detectable, as the enclosed reservoir bag fails to inflate. It is less obvious during spontaneous ventilation, and rebreathing results.

The Enclosed Magill breathing system seems to conform to the characteristics of an A type system during spontaneous ventilation. A fresh gas flow of between alveolar and minute ventilation is adequate, in most patients, if rebreathing is to be avoided. In the controlled mode it also has the functional characteristics of an A system. However, provided that a minute ventilation in excess of fresh gas flow (in this study 120 ml kg^{-1}) is used, end-tidal carbon dioxide is determined by the fresh gas flow and a value between 70 and 100 ml kg^{-1} min^{-1} should be appropriate to maintain normocapnia. The breathing system may be used in both modes and can therefore be described as a universal system.

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COMPARISON OF THE BAIN AND THE ADE SYSTEMS DURING CONTROLLED VENTILATION IN ADULTS

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SUMMARY

It has been suggested that Humphrey's ADE system may be an improvement on the Bain system. To compare their efficiencies we have studied 20 anaesthetized adults who had controlled ventilation established with a circle absorber system at a $\dot{V}_E$ sufficient to maintain normocapnia. Patients were then randomly allocated to either a Bain or an ADE system. Fresh gas flow was sufficient to keep $P_{E'CO_2}$ constant for 30 min. The other circuit was then used for an additional 30 min. The required FGF was 54 ml kg^{-1} min^{-1} for the Bain system, compared with 67 ml kg^{-1} min^{-1} for the ADE system. We conclude that, during controlled ventilation, the ADE system is 25% less efficient than the Bain system.

Since Ayre's original description of the "T-piece" system [1], anaesthetists have introduced modifications to facilitate different aspects of anaesthetic management. One variation on this theme is Humphrey's "ADE" system [2] (Mercury Enterprise, Ft. Lauderdale, FL) designed to facilitate changing from a "Mapleson D or E" configuration during controlled ventilation to a "Mapleson A" mode for spontaneous ventilation [3]. A recent study [4] suggested that, when a fresh gas flow (FGF) of 70 ml kg^{-1} min^{-1} was used, this device was as effective for controlled ventilation in adult patients as the Bain system, which is another variant of the Mapleson D. Because an FGF of 70 ml kg^{-1} min^{-1} is considerably in excess of the FGF requirements for maintaining normocapnia during controlled ventilation with the Bain system in adults [5], we have studied the efficiencies of the two systems at the minimum FGF required to maintain normocapnia.

PATIENTS AND METHODS

We studied 20 adult patients (mean (SD) age 52 (19) yr; 15 males), ASA class I, undergoing elective surgery. The study was approved by the local Institutional Review Board and written informed consent was obtained. Anaesthesia was induced with thiopentone and maintained with 0.5–0.6% isoflurane and 60% nitrous oxide in oxygen. Tracheal intubation was facilitated with a competitive neuromuscular blocking drug and ventilation was controlled using a Drager Narcomed II anaesthesia ventilator with an in-circle carbon dioxide absorber. Tidal volume was set at 10 ml kg^{-1} and a 1:3 inspiratory to expiratory ratio. Inspired and end-tidal gas concentrations were measured with a calibrated Perkin–Elmer mass spectrometer with sampling from a catheter placed in the lumen of the tracheal tube (rate of sampling 200 ml min^{-1}; the sample was not returned to the system); minute ventilation was determined with a calibrated respirometer (Boehringer Corp. of Pennsylvania, U.S.A.) placed at the tracheal tube adaptor. Heart rate was determined from the cardiotachometer of a standard electrocardiograph lead II. Arterial pressure was measured by sphygmomanometry, temperature with a nasopharyngeal thermocouple, and arterial blood-gas tensions with a Corning Model 178 blood-gas analyser.

During controlled ventilation with the circle system, the rate of ventilation was adjusted to maintain end-tidal carbon dioxide partial pressure between 4.7 and 5.3 kPa (mean frequency $f = 5.9$

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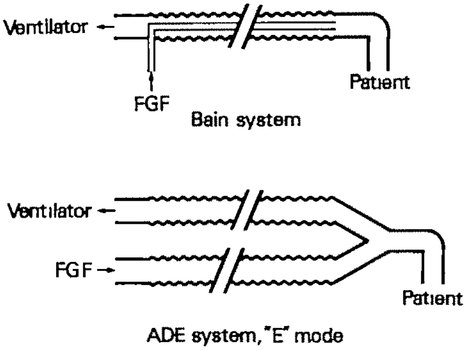

FIG. 1. Comparative configurations of the Bain and ADE systems.

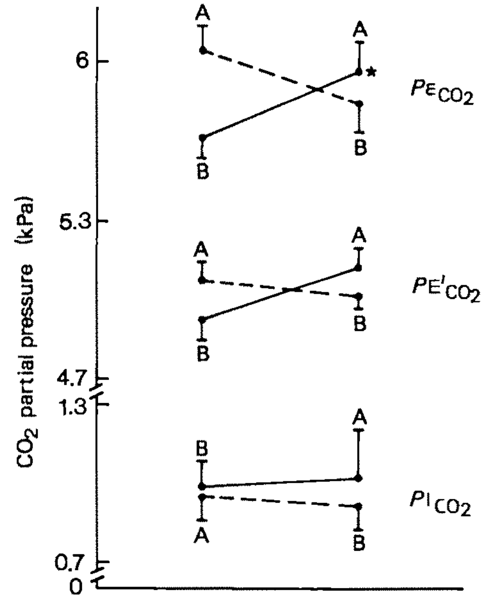

FIG. 2. Differences in carbon dioxide partial pressures associated with changing from the ADE (A) to the Bain (B) system (---) and *vice versa* (——). Fresh gas flow was held constant in each situation: FGF for B to A = 54 (SEM 2.5) ml kg^{-1} min^{-1}; FGF for A to B = 67 (3.8) ml kg^{-1} min^{-1}. The Bain circuit proved to be more efficient than the ADE circuit.

(SEM 0.2) b.p.m.). Patients were allocated randomly to receive anaesthetic gases via either the Bain or the ADE system. The configurations of the systems are shown in figure 1. Both systems were connected directly to the tracheal tube. The apparatus deadspace was approximately 40 ml with both systems. The Bain system was connected to the anaesthesia machine using a simple adaptor with a pressure manometer and bagmount. The ventilator was attached to the expiratory limb of the system with the exhaled gas "pop-off" located in the ventilator. Thus there was no return of waste gases from the ventilator to the system. The non-coaxial version of the single lever ADE system was set in the "E" mode, with the lever in the "down" position. As with the Bain system, the ventilator was attached to the expiratory limb. The Drager anaesthesia machine has an audible low pressure sensor, which was connected to the FGF tube for both the Bain and the ADE systems. Minute ventilation (mean 58 (SEM 2.0) ml kg^{-1} min^{-1}) was kept constant while FGF was adjusted to maintain end-tidal carbon dioxide partial pressure constant between 4.7 and 5.3 kPa with both systems. After 30 min, each patient received anaesthetic gases from the alternative system. FGF and $\dot{V}_E$ were held constant for an additional 30 min. At the end of the study, all patients were returned to ventilation with the circle system at the same FGF and $\dot{V}_E$ as had been used with either the Bain or the ADE system. Cardiovascular and ventilatory measurements were recorded at 10-min intervals during each 30-min observation period. These values and blood-gas tensions were tabulated at the end of each 30-min period. Mean values were obtained at the end of 30 min with the first valveless system and were compared with those obtained after 30 min with the other system, using Student's *t* test for paired data. $P < 0.05$ was regarded as significant.

RESULTS

Among the patients randomly allocated first to the Bain system, the mean (SEM) FGF required to maintain an end-tidal carbon dioxide partial pressure in the range 4.7–5.3 kPa was 54 (2.5) ml kg^{-1} min^{-1}, as was suggested originally by Bain and Spoerel [8]. In contrast those anaesthetized first with the ADE system required an FGF of 67 (3.8) ml kg^{-1} min^{-1} ($P < 0.05$) to maintain the same end-tidal carbon dioxide partial pressure. During anaesthesia with the ADE system, the mean (SEM) end-tidal isoflurane concentration was 0.57 (0.04) %. During anaesthesia with the Bain system, the end-tidal isoflurane concentration was 0.58 (0.04)%. No change in any cardiovascular measurement was observed.

The changes in carbon dioxide tensions observed 30 min after patients were switched from either the Bain to the ADE system or *vice versa* are shown in figure 2. Arterial carbon dioxide increased significantly when patients were changed from the Bain system to the ADE circuit. The opposite effect (a decrease in Pa_{CO_2}) was observed when patients were switched from the ADE circuit to the Bain system. As expected, end-tidal and inspired carbon dioxide partial pressures paralleled the changes in arterial carbon dioxide partial pressures as patients were changed from one system to the other.

DISCUSSION

Valveless anaesthetic systems are used widely for paediatric anaesthesia and for some specialized procedures such as diagnostic imaging of the head (CT and MRI scanning) where there is a long distance between the anaesthetic machine and the patient's airway. In addition, because these systems can be used in place of expensive anaesthesia machines, they are extremely popular in the third world [6]. As expense has become a significant consideration both in the U.S. and elsewhere, it seems reasonable to use these devices in a manner that conserves expensive anaesthetic gases.

Controlled ventilation as used in this study, with a large tidal volume and a long pause between ventilatory cycles, permits wash-out of exhaled gases and creates a "buffer" of fresh gas for the next inspiratory cycle, as postulated by Mapleson [3] and documented by Harrison [7]. It is this combination, and the availability of carbon dioxide monitoring devices, that makes the use of the traditional 70 ml kg^{-1} min^{-1} FGF rate for these systems wasteful in adult patients receiving controlled ventilation.

Most published studies of the Bain system have utilized minute ventilation of 120–140 ml kg^{-1} min^{-1} based on requirements predicted by the Radford nomogram [8]. These values are far in excess of those required for maintenance of normocapnia when a carbon dioxide absorber is used. Because of the high minute ventilation used in these previous studies, a high fresh gas flow (70 ml kg^{-1} min^{-1}, equal to 0.6 of expiratory minute volume, $\dot{V}_E$) was thought necessary to maintain normocapnia [9]. In the present study, where required minute ventilation during general anaesthesia was first established with a circle absorber system, we were able to maintain normocapnia with a much lower fresh gas flow, even though the ratio of FGF to $\dot{V}_E$ was 0.9 for the Bain, and 1.2 for the ADE system.

The data indicate clearly that, during controlled ventilation, the Bain system permits a 24% lower minimum FGF rate than does the ADE circuit. During an anaesthetic procedure of long duration, this could account for a considerable saving in the volume and cost of anaesthetic gases utilized. When the ADE system is used at an FGF rate of 70 ml kg^{-1} min^{-1} as has been recommended for the Bain circuit [4], it is not surprising that its performance does not differ from that of the Bain system. It is only when FGF is reduced to its lowest safe limits that the greater efficiency of the Bain system becomes apparent. Presumably, if still lower FGF and higher carbon dioxide partial pressures were studied, the greater efficiency of the Bain system would become even more obvious, but this study was designed specifically to maintain carbon dioxide partial pressures within the physiological range.

In conclusion, the Bain system may be used safely with an FGF that is significantly lower than has been suggested previously, provided controlled ventilation with a long expiratory pause is used. Furthermore, we found that the Bain system is 24% more efficient than the ADE circuit at conserving anaesthetic gases.

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COMPARISON OF THE MAGILL AND LACK ANAESTHETIC BREATHING SYSTEMS IN ANAESTHETIZED PATIENTS

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The fresh gas flow rate required to prevent rebreathing in the Mapleson A (Magill) anaesthetic breathing system has been studied extensively in anaesthetized patients [1] and conscious volunteers [2, 3]. These authors agreed with the conclusions of the theoretical analysis performed by Mapleson [4] and found that rebreathing did not occur until fresh gas flow was reduced to approximately alveolar minute volume. More recently, Humphrey [5] has reported that a fresh gas flow rate of 71.5 (SEM 2.70) ml kg^{-1} min^{-1} is required to induce rebreathing in anaesthetized patients. However, Dixon, Chakrabarti and Morgan [6] reported the onset of rebreathing at a mean fresh gas flow rate of 69.3 (SD 12) ml kg^{-1} min^{-1} in conscious volunteers and 56.5 (SD 15.9) ml kg^{-1} min^{-1} in lightly anaesthetized subjects.

The fresh gas flow rate required to prevent rebreathing with the coaxial version of the Mapleson A (Lack system) has also been the subject of controversy. Barnes, Conway and Purcell [7] noted that the Lack system was somewhat less efficient than the non-coaxial A system in conscious volunteers. Norman, Nott and Walters [8] showed the two systems to be equally efficient. Humphrey [5] claimed that the Lack system is considerably superior to the conventional A system, requiring a mean fresh gas flow rate of 51.30 (SEM 2.01) ml kg^{-1} min^{-1} to induce rebreathing. Because controversy exists concerning the fresh gas flow rate required to prevent rebreathing in the conventional and coaxial A systems, we have compared them at fresh gas flow rates of approximately 50 ml kg^{-1} min^{-1} and 70 ml kg^{-1} min^{-1} in lightly anaesthetized patients.

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SUMMARY

The Magill and Lack anaesthetic breathing systems were compared by measuring inspired and expired carbon dioxide concentrations and expired minute volumes in lightly anaesthetized, unstimulated subjects. There were no significant differences between the two breathing systems at fresh gas flow rates of approximately 50 and 70 ml kg^{-1} min^{-1}. Inspired carbon dioxide concentrations increased in one of six subjects at the higher fresh gas flow rate using the Magill system and in two using the Lack system. Inspired carbon dioxide concentration did not increase in only one of six subjects at the lower fresh gas flow rate with both systems. Expired carbon dioxide concentrations and expired minute volume increased in the majority of subjects at both fresh gas flow rates using each system. We conclude that a fresh gas flow rate greater than 70 ml kg^{-1} min^{-1} (which approximated to alveolar minute volume in our subjects) should be supplied to the Magill and Lack breathing systems.

PATIENTS AND METHODS

Twenty-four healthy adults (ASA I) were included in the study. They required general anaesthesia and tracheal intubation. They gave informed consent to the study, which was approved by the Hospital Ethics Advisory Committee. Premedication was with diazepam 10 mg by mouth 2 h before surgery and anaesthesia was induced with thiopentone 5 mg kg^{-1}. Suxamethonium 1 mg kg^{-1} was administered and the larynx and trachea were sprayed with 4% lignocaine 3 ml. Tracheal intubation was performed using a cuffed tracheal tube.

The patients breathed 1% halothane and 70% nitrous oxide in oxygen for a period of 10–20 min.

TABLE I. *Expired minute volume (litre)*

Group	End of control period	End of experimental period	Fresh gas flow rate (ml kg^{-1} min^{-1})	Body mass (kg)
Magill	7.0	7.2	71.2	52.2
(70 ml kg^{-1} min^{-1})	6.8	7.2	70.0	60.0
	4.4	4.4	70.9	55.0
	5.6	5.8	68.8	61.2
	5.4	6.0	69.2	65.0
	5.2	6.0	72.7	55.0
Lack	4.8	5.2	69.8	53.0
(70 ml kg^{-1} min^{-1})	6.8	8.0	69.8	53.0
	6.4	7.0	69.1	55.0
	8.2	8.8	69.8	86.5
	5.6	6.0	68.0	60.0
	5.6	6.4	68.0	47.0
Magill	6.2	6.0	50.0	62.0
(50 ml kg^{-1} min^{-1})	7.2	9.0	49.4	87.0
	6.0	7.2	51.5	66.7
	5.8	7.5	50.7	63.0
	8.0	11.2	50.0	72.0
	6.8	7.6	46.4	65.0
Lack	6.0	6.4	50.0	58.0
(50 ml kg^{-1} min^{-1})	6.8	8.8	49.6	70.5
	6.6	11.5	50.7	63.0
	5.2	10.0	48.4	62.0
	6.4	8.0	50.6	75.0
	5.8	7.0	50.0	62.8

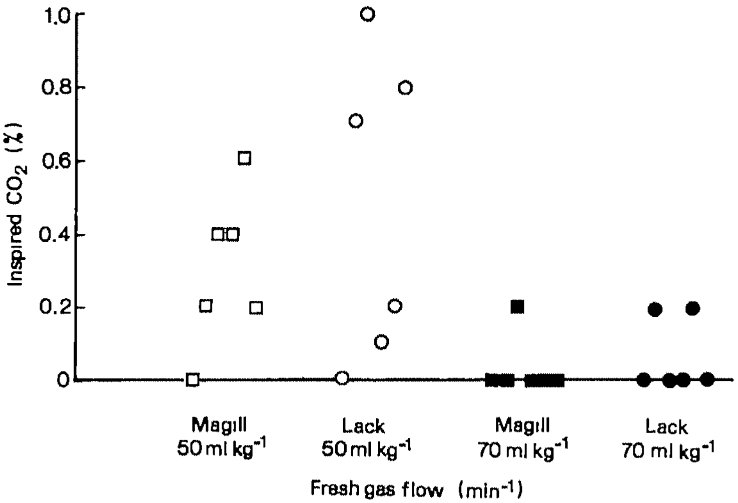

FIG. 1. Inspired carbon dioxide concentrations in the Magill and Lack breathing systems at two fresh gas flow rates.

During this time the gas mixture was delivered at a rate in excess of 100 ml kg^{-1} min^{-1}, via a Magill attachment, to all subjects. End-tidal carbon dioxide concentration was measured continuously using a capnograph (Hewlett-Packard), expired minute volume using an electronic spirometer (Wright) and ventilatory flow using a pneumotachograph (Fleisch). The total apparatus deadspace was 34 ml. Measurements were displayed on a pen recorder (Brush) and recorded on FM tape. When stabilization had occurred, shown by a constant value of expired minute

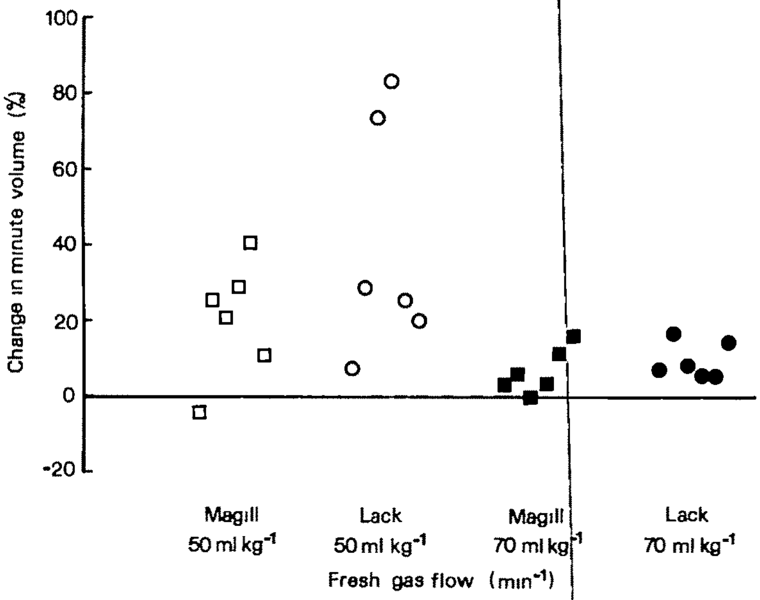

FIG. 2. Changes in minute volume in the Magill and Lack breathing systems at two fresh gas flow rates.

volume, fresh gas flow was reduced to either 50 ml kg^{-1} min^{-1} or 70 ml kg^{-1} min^{-1}. The subjects had previously been assigned randomly to one of four groups: Magill, 70 or 50 ml kg^{-1} min^{-1}; Lack, 70 or 50 ml kg^{-1} min^{-1}. Fresh gas was supplied from a Boyle anaesthetic machine with the rotameters set to the graduation which approximated most nearly the above flows. Rotameter calibration was checked using a dry gas meter. The subjects breathed at the designated flow rates for a period of 20 min. After completion of the study, surgery commenced. A single Magill breathing system and a single Lack breathing system were used throughout the study.

RESULTS

Expired minute volumes immediately before reduction of fresh gas flow to experimental values and at the end of the experiment, and exact fresh gas flow rates in terms of body weight, are listed in table I.

At the higher fresh gas flow rate, one patient in the Magill group and two in the Lack group had carbon dioxide in the inspired gas. At the lower fresh gas flow rate, inspired carbon dioxide did not increase in only one patient in each group (Magill and Lack) (fig. 1). Minute volume (fig. 2) and end-tidal carbon dioxide concentration (fig. 3) increased in the majority of patients in all four groups. A representative capnograph with pneumotachograph signal for a patient without an increase in inspired carbon dioxide at a fresh gas flow of 70 ml kg^{-1} min^{-1} is shown in figure 4.

The results were analysed using non-parametric statistics (Mann–Whitney *U* test and Fisher Exact probability test). There were no significant differences between the Magill and Lack systems.

DISCUSSION

The functional characteristics of simple breathing systems without carbon dioxide absorption have been defined by the fresh gas flow rate required to prevent rebreathing.[1] Although some rebreathing is possible potentially in all but truly open breathing systems, it has little physiological consequence until the degree of rebreathing is such that carbon dioxide re-enters the alveolar space. In lightly anaesthetized subjects this causes an increase in minute volume to maintain normal alveolar carbon dioxide concentration [9]. In more deeply anaesthetized subjects this response is obtunded, so alveolar carbon dioxide concentration increases if the fresh gas flow rate is less than that required to prevent rebreathing.

In spontaneously breathing anaesthetized subjects, the presence or absence of rebreathing cannot be detected merely by measuring arterial

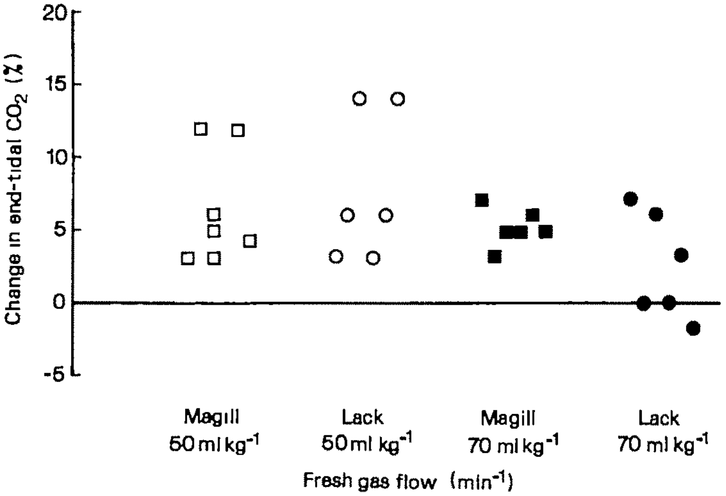

FIG. 3. Changes in end-tidal carbon dioxide concentration in the Magill and Lack breathing systems at two fresh gas flow rates.

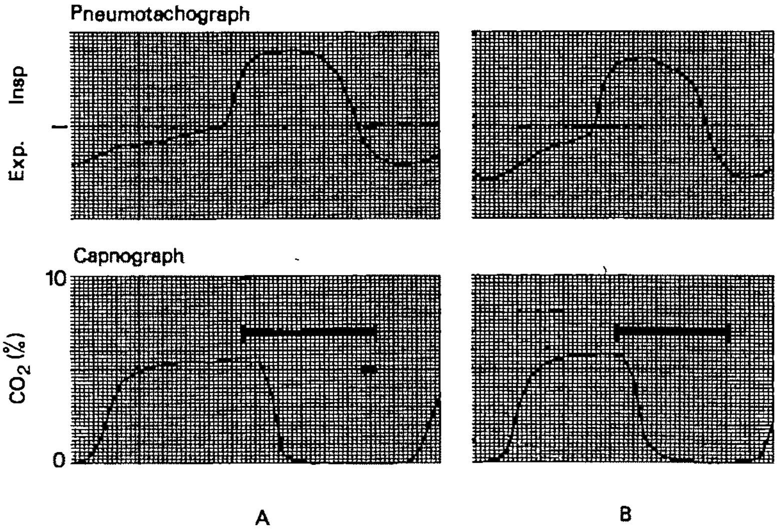

FIG. 4. Pneumotachograph and capnograph traces. A: Fresh gas flow 100 ml kg^{-1} min^{-1} to Lack breathing system. B: Fresh gas flow 70 ml kg^{-1} min^{-1} to Lack breathing system. The bar indicates the inspiratory period, corrected for signal delay.

carbon dioxide tension, or be recognized easily by monitoring inspired carbon dioxide concentration. In order to detect rebreathing, it is necessary to monitor both inspired carbon dioxide concentration and expired minute volume. In this study we have not attempted to determine the fresh gas flow at which rebreathing can be detected. We have determined only changes in end-tidal carbon dioxide concentration and expired minute volume at two fresh gas flow rates. These were selected because Humphrey [5] reported that the Lack system required approximately 51 ml kg^{-1} min^{-1}, and the Magill 72 ml kg^{-1} min^{-1}, to just induce rebreathing (as defined by an increase of 0.27 kPa in inspired carbon dioxide concentration).

When the fresh gas flow rate approximated to 70 ml kg^{-1} min^{-1}, rebreathing (demonstrated by an increase in the minimum inspired carbon dioxide concentration) occurred in one subject breathing through the Magill attachment and two using the Lack system. However, changes in end-tidal carbon dioxide concentration and expired minute volume occurred at this fresh gas flow rate in the majority of patients. The attainment of zero inspired carbon dioxide concentration does not indicate that rebreathing is not taking place. Figure 4 is a representative example of the change in the capnograph that occurs when fresh gas flow approximates to 70 ml kg^{-1} min^{-1}, in each breathing system. Although the inspired carbon dioxide concentration reaches zero, it does so for a smaller percentage of the inspiratory period when fresh gas flow is 70 ml kg^{-1} min^{-1} (fig. 4B) than it does when compared with control (fig. 4A). This inspired carbon dioxide load may be the cause of the reported increases in minute volume and end-tidal carbon dioxide concentration. Although the changes in end-tidal carbon dioxide concentration and expired minute volume were not statistically significant, a fresh gas flow rate of approximately 70 ml kg^{-1} min^{-1} may represent a threshold below which frank rebreathing commences. When the fresh gas flow rate was approximately 50 ml kg^{-1} min^{-1}, the inspired carbon dioxide concentration was variable in both the Magill and Lack groups.

Inspired carbon dioxide concentrations did not increase in one subject in each group, even at the lower fresh gas flow rate. However, the inspired carbon dioxide concentration reached zero for only a fraction of the inspiratory period. The wide variation of inspired carbon dioxide concentration may indicate that factors other than fresh gas flow rate determine the onset and degree of rebreathing.

In respect of the Magill attachment our study is consistent with the findings reported by Dixon, Chakrabarti and Morgan [6], who found that rebreathing (as defined by increases in carbon dioxide concentration and expired minute volume) commenced when the fresh gas flow rate reached a mean of 56 ml kg^{-1} min^{-1} in anaesthetized subjects. In their study, one patient rebreathed at a fresh gas flow rate of 100 ml kg^{-1} min^{-1}, but the remainder did not rebreathe until the fresh gas flow rate was well below 70 ml kg^{-1} min^{-1}. In contrast, Humphrey [5] reported that a mean fresh gas flow rate of 71.5 ml kg^{-1} min^{-1} was required to induce rebreathing in anaesthetized patients. These two studies were performed on patients during surgery, and the anaesthetic techniques differed. In our study all measurements were made before surgery commenced. In five of six patients, inspired carbon dioxide concentrations did not increase when fresh gas flow rate was approximately 70 ml kg^{-1} min^{-1}.

These findings are not difficult to reconcile. It can be misleading to report mean figures. If Humphrey's data are examined, it may be seen that four of 10 patients did not begin to rebreathe until fresh gas flow rate was 65 ml kg^{-1} min^{-1} or less and, of the remainder, five began to rebreathe at fresh gas flow rates of just over 70 ml kg^{-1} min^{-1}. It is not possible to relate the fresh gas flow rates quoted to the control minute volume, and hence alveolar minute volume, in either of the above studies. In our study a fresh gas flow rate of 70 ml kg^{-1} min^{-1} approximated to 70 % of resting minute volume and, hence, was equivalent to alveolar minute volume.

With respect to the Lack system, our study refutes the findings of Humphrey. Five of our six patients had evidence of rebreathing when the fresh gas flow rate approximated to 50 ml kg^{-1} min^{-1}. Humphrey reported that fresh gas flow rate could be reduced with the Lack system to 51 ml kg^{-1} min^{-1}, to equal the efficiency of the Magill with a fresh gas flow rate of 71 ml kg^{-1} min^{-1}. Jonsson [10] has also examined the fresh gas flow rate required to prevent rebreathing when the Lack system is in use, with an experimental model and in anaesthetized patients. He found that a fresh gas flow rate of 85 ml kg^{-1} min^{-1} was required in the model to prevent rebreathing. In anaesthetized subjects, he found evidence of rebreathing in 55 % of subjects when the fresh gas flow rate was 70 ml kg^{-1} min^{-1} and in 92 % of subjects when the fresh gas flow rate was 55 ml kg^{-1} min^{-1}. He expressed difficulty reconciling his findings to those of Humphrey, and agreed with Conway [11] that the differences probably demonstrated variation in experimental technique. Certainly differences in experimental technique may account for some of the discrepancies between the reported results. On the basis of our present study, we suggest that the fresh gas flow rate needed to prevent rebreathing in both the Magill and Lack systems approximates to alveolar minute volume. We recommend that fresh gas flow rate in excess of 70 ml kg^{-1} min^{-1} should be used in both systems.

One of the features of the studies reported is that the fresh gas flow rate (ml kg^{-1} min^{-1}) needed to prevent rebreathing appears to differ in conscious and anaesthetized subjects. This is demonstrated in the study reported by Dixon and his colleagues [6], who showed that there was a marked difference in the fresh gas flow rate needed to prevent rebreathing in conscious volunteers and anaesthetized patients.

There is also a difference from our reported findings with the Lack system in awake volunteers, in whom the fresh gas flow rate needed to prevent rebreathing was of the order of minute volume [7], whereas in the present study fresh gas flow rates approximating to alveolar minute volume were adequate. This difference may be caused by anaesthesia, change in breathing pattern or because of differences in carbon dioxide production.

ACKNOWLEDGEMENTS

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EFFECT OF ORAL DOXAPRAM ON MORPHINE-INDUCED CHANGES IN THE VENTILATORY RESPONSE TO CARBON DIOXIDE

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SUMMARY

A double-blind crossover volunteer trial has been carried out to determine if oral doxapram reduces the respiratory depression caused by morphine 0.12 mg kg^{-1} i.m. Doxapram was given to the subjects 90 min before the morphine and significantly reduced the displacement of the ventilatory response to carbon dioxide caused by the morphine. This occurred despite the fact that the plasma concentrations of doxapram were significantly lower when the subject had been given morphine than when a placebo injection had been administered. Doxapram alone in doses of 300 mg and 600 mg did not alter significantly the respiratory variables measured in this study.

Doxapram is a potent respiratory stimulant which has been used for many years in the management of acute and chronic ventilatory failure caused by drugs or lung disease. Studies have confirmed its usefulness in postoperative respiratory depression [1], respiratory failure caused by chronic obstructive lung disease [2] and respiratory depression and apnoea of prematurity in the newborn [3, 4]. When given as an i.v. bolus or prolonged infusion, doxapram increases the slope of the ventilatory response to isocapnic hypoxia and to progressive hypercapnia in normal volunteers [5]. Doxapram i.m. has been shown to reduce the displacement of the hypercapnic ventilatory response caused by pethidine given to volunteers [6].

Gupta and Dundee [7, 8] have demonstrated, in patients receiving large doses of morphine following upper abdominal surgery, that an i.v. infusion of doxapram restored the depressed minute volume without affecting analgesia. A reduced incidence of respiratory complications was observed also.

A pharmacokinetic study [9] demonstrated that doxapram given as an enteric coated capsule was absorbed rapidly after an initial delay and had systemic availability of approximately 60% (range 49–86%). After oral administration the plasma half-life ranged from 6.6 h to 9.4 h (mean 7.5 h).

Two unpublished trials carried out in France (J. Charpin, 1973; J. Germouty, 1978; unpublished observations) suggested that the oral preparation of doxapram (enteric coated capsule) causes significant and sustained respiratory stimulation (as measured by changes in Pa_{O_2}, Pa_{CO_2}, pH and haemoglobin oxygen saturation) in patients suffering from chronic respiratory failure.

There have been several encouraging reports of postoperative benefits following parenteral doxapram, including reduction in duration of hospital stay [1]. It is possible that administration of doxapram by mouth before operation might have similar beneficial effects. However, establishment of the efficacy of an oral preparation in controlled conditions is a prerequisite to any studies in the postoperative setting. Thus a volunteer study has been conducted to compare the effects of two different single doses of doxapram by mouth on the respiratory depression caused by i.m. morphine.

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SUBJECTS AND METHODS

The study was approved by the Hospital Ethics Committee and written informed consent was obtained from 12 volunteer subjects who were healthy as defined by normal medical history, physical examination, blood counts and blood biochemical profile.

Doxapram and morphine were given in a placebo-controlled and double-blind regimen. Each subject attended on four days (placebo/placebo, placebo/morphine, doxapram/placebo and doxapram/morphine), each occasion separated by a period of at least 2 weeks. Subjects were allocated randomly to receive doxapram 300 mg or 600 mg.

Volunteers were fasted overnight, although fruit juice, but not drinks containing caffeine, was allowed for up to 2 h before the start of the trial. All experiments were conducted in a quiet, single-bed side ward. Baseline values were recorded for all the variables studied. The subjects were given two capsules (placebo or doxapram) and, 1 h later, all variables were measured again. An i.v. cannula was inserted into a forearm vein and 10 ml of blood withdrawn. At 90 min, the subjects received an i.m. injection of either morphine 0.12 mg kg^{-1} or 0.9 % saline of equivalent volume into a deltoid muscle. At 2, 3, 4, 5, 6 and 8 h, measurements were repeated and blood samples taken.

The tests were performed in the following sequence. The subjects recorded their feeling of sedation on a 10-cm visual analogue line (marked (wide awake..... almost asleep)). Oral temperature, heart rate and arterial pressure (Copal digital sphygmomanometer (UA-251)) were recorded. Minute volume, rate of ventilation and tidal volume were measured in the sitting position using a mouth piece connected to a closed circuit bell spirometer (Ealing) containing air (total volume including tubing, 11.5 litre). End-tidal carbon dioxide ($P_{E'CO_2}$) was measured continuously with an infra-red analyser (Morgan) and a continuous trace obtained from a pen recorder (Rikadenki). Using the same equipment but with the spirometer bell filled with 5% carbon dioxide in oxygen and the soda-lime carbon dioxide absorber removed, ventilatory response to hypercapnia produced by rebreathing was recorded over 5 min or until a minute volume of at least 30 litre was obtained. End-tidal P_{CO_2} values were between 7 and 9 kPa at this time. After the first 1 min (to allow for equilibration) the minute volume was plotted against $P_{E'CO_2}$ at 30-s intervals. The slope of the plot was calculated using the method of least squares and the $P_{E'CO_2}$ at 30 litre minute volume (30 litre intercept) recorded. Displacement of the plot was measured in addition to the slope, as some authors have reported that morphine tends to displace the plot rather than change its slope [10]. The value of 30 litre min^{-1} was chosen because it intersected the lines for all subjects without extrapolation.

Any side effects reported by the subject were recorded.

All blood samples were put in lithium–heparin tubes, centrifuged and the plasma removed and frozen within 20 min of being taken. Plasma concentrations of doxapram were assayed by gas–liquid chromatography [9].

Pharmacodynamic data were analysed by repeated measures analysis of variance using the GLIM3 and BMDP statistical computer packages at the University of Manchester Regional Computing Centre. These packages make both between-subjects and within-subject comparisons. If differences were detected between the means, the Least Significant Difference statistic (LSD) was calculated to determine which means were significantly different. Otherwise results are expressed as mean (SEM).

RESULTS

There were no significant differences between the age or weight of the subjects given doxapram 300 mg and doxapram 600 mg, although the male : female ratio was somewhat different (table I).

Doxapram alone produced no ventilatory changes which distinguished the group significantly from the placebo group. Although some individuals appeared to have increased sensitivity to carbon dioxide, this did not correlate with plasma concentrations of doxapram.

Doxapram was detectable in the plasma of two subjects 1 h after administration of doxapram 300 mg but, in general, plasma concentration began to increase after 3 h. Peak concentrations were obtained 6–8 h after the oral administration (fig. 1). Although the 600-mg dose produced higher plasma concentrations than did the 300-mg dose, this just failed to reach statistical significance in the small group of six subjects. The peak concentrations were 0.19–0.33 µg ml^{-1} for the 300-mg dose and 0.42–1.50 µg ml^{-1} for 600-mg dose.

TABLE I. *Details of volunteers*

Subject No.	Sex	Age (yr)	Weight (kg)	Arterial pressure systolic/ diastolic (mm Hg)
Doxapram 300 mg				
2	M	29	67	115/70
3	F	29	65	118/77
4	M	28	79	130/80
8	F	29	54	110/70
9	M	28	69	122/66
12	M	32	71	120/78
Mean		29	67	119/74
Doxapram 600 mg				
1	F	30	85	121/88
5	F	30	68	116/81
6	M	32	83	125/80
7	F	26	56	132/82
10	F	26	65	117/75
11	M	28	67	107/72
Mean		29	71	120/80

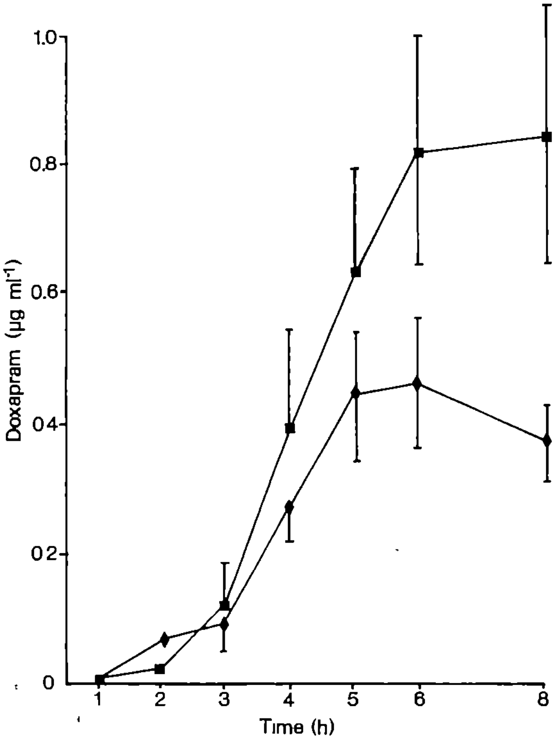

FIG. 1. Mean (SEM) plasma concentrations of doxapram in subjects given doxapram 300 mg (◆) or 600 mg (■) by mouth in enteric-coated capsules.

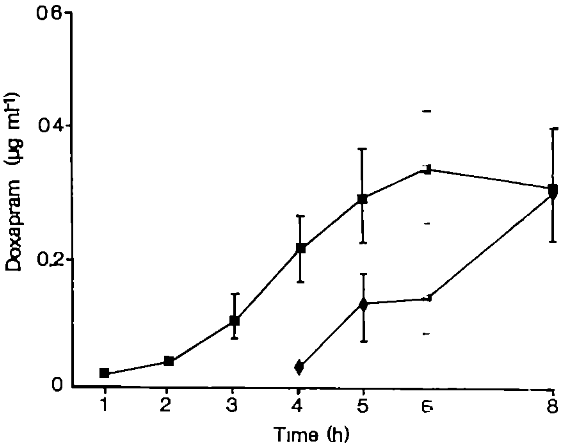

FIG. 2. Mean (SEM) plasma concentrations of doxapram in subjects given doxapram 300 mg (◆) or 600 mg (■) by mouth, followed 90 min later by morphine 0.2 mg kg^{-1} i.m.

The administration of morphine 90 min after oral doxapram reduced significantly ($P < 0.05$) the plasma concentration of doxapram (fig. 2) and delayed the time until doxapram was detectable in the plasma. One subject's plasma contained only traces of doxapram 6 h and 8 h after doxapram 600 mg had been swallowed. Statistical analysis of all the measured variables demonstrated no dose dependency for the effect of doxapram. In view of this, the doxapram groups have been combined for subsequent analysis to give group sizes of 12.

As expected, morphine alone displaced the ventilatory response to carbon dioxide to the right, this being significant ($P < 0.001$) from the 2-h reading (30 min after the morphine injection) to the 8-h reading. Subjects given doxapram and morphine also exhibited significant displacement of the ventilatory response to carbon dioxide, but this was significantly less ($P < 0.05$) than that produced by morphine alone at all times of measurement, with the exception of the 5-h reading (table II).

A transitory decrease (33 %) in the slope of the ventilatory response to carbon dioxide was seen 30 min after the injection of morphine (table III). This was reduced slightly (26 %) in subjects given doxapram in addition. However, full statistical analysis of the results demonstrated that slope followed a log-normal distribution and that analysis of variance of the transformed data yielded a probability of only 0.057 that morphine caused a change in slope.

TABLE II. *Mean intercept (kPa) of the ventilatory response to carbon dioxide at 30 litre minute volume in subjects given morphine 0.12 mg kg^{-1} i.v. and doxapram 300 and 600 mg by mouth. Morphine was given between the 1- and 2-h readings. Least Standard Difference (LSD) between any two means = 0.53; standard deviation within subjects = 0.43. *Significantly different from placebo ($P < 0.01$); †Morphine+doxapram significantly less than morphine alone ($P < 0.05$)*

	Time (h)							
Treatment	Base	1	2	3	4	5	6	8
Placebo	6.75	6.81	6.78	6.63	6.96	6.92	6.88	6.79
Morphine	6.94	7.03	8.37*	8.49*	8.55*	8.11*	8.29*	7.98*
Doxapram	6.80	6.86	6.88	6.91	6.91	7.12	6.90	6.91
Morphine+ doxapram	6.54	6.63	7.49*†	7.54*†	7.48*†	7.79*	7.40*†	7.44*†

TABLE III. *Mean slope (1 litre kPa^{-1}) of the ventilatory response to carbon dioxide in subjects given morphine 0.12 mg kg^{-1} i.m. and doxapram 300 and 600 mg by mouth. Morphine was given between the 1- and 2-h readings. Statistical analysis was carried out on data transformed by taking natural logarithms. The mean values quoted are for the detransformed values. Least Significant Difference (LSD) between any two means = 1.50; standard deviation within subjects = 0.23*

	Time (h)							
Treatment	Base	1	2	3	4	5	6	8
Placebo	14.1	13.8	14.1	14.7	12.3	11.8	14.5	13.4
Morphine	13.8	12.6	9.2	11.5	10.2	10.2	9.6	10.6
Doxapram	12.9	12.3	12.3	11.7	12.1	11.3	13.3	12.1
Morphine+ doxapram	14.8	14.3	11.2	11.2	11.2	12.1	13.3	11.0

TABLE IV. *Mean minute ventilation (litre) in subjects receiving morphine 0.12 mg kg^{-1} i.m. and doxparam 300 and 600 mg by mouth. Morphine was given between the 1- and 2-h readings. Least Significant Difference (LSD) between any two means = 2.60; standard deviation within subjects = 2.1. *Significantly different from placebo ($P < 0.05$)*

	Time (h)							
Treatment	Base	1	2	3	4	5	6	8
Placebo	9.6	10.2	10.4	10.8	12.2	11.6	11.0	11.5
Morphine	9.9	10.7	9.0	7.8*	8.4*	8.4*	8.7	10.6
Doxapram	9.7	10.7	11.1	11.0	11.3	9.9	10.7	11.5
Morphine+ doxapram	10.6	10.6	9.9	9.9	9.6*	8.0*	9.2	10.4

Of the other respiratory variables, only minute ventilation breathing air showed significant changes ($P = 0.0075$) (table IV). Subjects had higher mean minute ventilation when treated with doxapram and morphine than when they were given morphine alone, but this difference did not reach statistical significance.

Morphine increased sedation scores from a mean of 16 mm on the analogue scale to 30 mm and this was statistically significant between the 3- and 6-h readings, inclusive ($P < 0.01$). Although doxapram appeared to reduce sedation scores in morphine-treated subjects, this did not reach statistical significance because of the large within-subject variation in this measure.

Four female subjects experienced nausea, vomiting or both, 3–4 h after morphine alone, and three of these subjects experienced this side effect after the morphine–doxapram combination. No male subject reported nausea.

DISCUSSION

The mean of the individual peak plasma concentrations of doxapram was 0.48 (SEM 0.20) $\mu g\ ml^{-1}$ after administration of doxapram 300 mg by mouth. This is approximately 50% of the peak concentration of 0.96 (0.23) $\mu g\ ml^{-1}$ reported by Robson and Prescott [9], but the spread of results in both studies was such that the difference in values is not statistically significant. The rate of increase in plasma concentration of doxapram reported in the present study is slower than that reported by Robson and Prescott [9]. It is possible that this reflects some differences in the enteric coated capsule formulation in the 8 years or so between the two studies.

Plasma concentrations were higher in subjects given doxapram 600 mg, although only two subjects had values exceeding the 1 $\mu g\ ml^{-1}$ which is found in patients receiving doxapram by infusion at the manufacturer's recommended rate [9].

Calverley and colleagues [5] reported that doxapram infusions which maintained plasma concentrations greater than 1.5 $\mu g\ ml^{-1}$ caused increases in minute ventilation and increased the slope of the ventilatory response to hypercapnia. The low concentrations of doxapram achieved in the present study had no significant effects on ventilation when given in the absence or morphine.

The injection of morphine after doxapram administration delayed the appearance and reduced the peak concentration of doxapram in blood. Opioid analgesics have been shown by others to reduce the absorption of orally administered drugs [11, 12]. It had been hoped that 90 min prior treatment with oral doxapram might reduce this effect. It is apparent that a considerably longer oral pretreatment time would be required to fulfil this purpose, which would limit any potential usefulness of the morphine–oral doxapram combination.

Despite the low concentrations of doxapram achieved, significant reductions in the rightward displacement of the ventilatory response to carbon dioxide induced by morphine were observed in five of the six time intervals studied. Earlier work in the rabbit has demonstrated that doxapram has greater effects on ventilation in the presence of morphine than it does in its absence [13] and this study suggests that the same is true in man. It may be that doxapram is a more effective respiratory stimulant if the respiratory system is depressed. In the treatment of idiopathic apnoea of prematurity, plasma concentrations of doxapram as low as 0.4 $\mu g\ ml^{-1}$ have been found to be effective [14].

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Br. J. Anaesth. (1989), **62**, 164–167

PLAIN BUPIVACAINE: 0.5% OR 0.25% FOR SPINAL ANALGESIA?

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SUMMARY

Plain 0.5% bupvicaine 3 ml was compared with plain 0.25% bupivacaine 6 ml for spinal anaesthesia during transurethral surgery in 40 patients. The solutions were injected over 30 s at the L3/4 space with the patient in the sitting position. The patient was kept sitting for 2 min, supine for 5 min and then placed in the lithotomy position. No significant differences were found in onset time, extent of cephalad spread, duration of sensory or motor blockade, or side effects. The use of a 0.5% plain solution of bupivacaine did not appear to confer any advantage over the 0.25% solution.

Bupivacaine has been used successfully for spinal anaesthesia for more than 10 years [1, 2]. In most centres in Denmark, 3–4 ml of 0.5% plain solution of bupivacaine (without adrenaline) is preferred for spinal anaesthesia. The extent and duration of sensory block following subarachnoid injection of local anaesthetic are thought to depend on several factors, such as total dose [3, 4], site of injection [5, 6], position of the patient [6, 7] and volume of solution [3, 6, 8, 9].

To our knowledge, solutions of 0.5% and 0.25% plain bupivacaine have not been compared for spinal analgesia. We have therefore evaluated the effects of plain bupivacaine 15 mg given as 3 ml of 0.5% or 6 ml of 0.25% solution.

PATIENTS AND METHODS

We studied 40 men (age range 60–79 yr) scheduled to undergo transurethral resection of the prostate under spinal anaesthesia. None of the patients suffered from neurological disease or deformity of the spine, and no patient had a history of hypersensitivity to local anaesthetics. Informed consent was obtained from all patients and the study was approved by the local Ethics Committee.

The patients were allocated randomly to two groups: group 1 received plain 0.5% bupivacaine 3 ml without adrenaline (Marcaine, Astra Läkarmedel Ab, Sweden); group 2 received 0.25% bupivacaine 6 ml. Premedication consisted of diazepam 5–10 mg by mouth 1–2 h before operation. Isotonic saline 500 ml was infused i.v. rapidly before lumbar puncture was performed. All lumbar punctures were performed using a 25-gauge spinal needle and a midline approach at the L3/4 space with the patient in the sitting position. Injection time was 30 s. The patient was kept sitting for 2 min, then placed supine; 5 min later the patient was placed in the lithotomy position. Arterial pressure and heart rate were measured every 5 min and ECG was monitored continuously.

Segmental spread of sensory loss was tested in the midline with the pin-prick technique using a 20-gauge needle. Motor blockade was assessed by the "Bromage Scale" (scores 3–0) [10]. Testing was performed every 5 min for the first 30 min after administration of bupivacaine, and thereafter every 30 min until sensory blockade at L1 level had recovered and motor blockade was regressing (Bromage scale ≤ 2). The investigator undertaking these tests was unaware of the volume of local anaesthetic used.

Side effects were noted, and ephedrine 5 mg

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TABLE I. *Patient data (mean (SD))*

	0.5% Bupivacaine 3 ml	0.25% Bupivacaine 6 ml
Age (yr)	70.4 (5.9)	70.8 (6.4)
Height (cm)	171.5 (5.4)	173.4 (7.6)
Weight (kg)	73.9 (13.4)	75.1 (12.5)

was administered i.v. if systolic arterial pressure decreased by more than 25%.

Statistical analyses using Student's *t* test or the Mann–Whitney test were performed as appropriate. $P < 0.05$ was considered significant.

RESULTS

There was no significant difference between the two groups in respect of patient age, height or weight (table I).

Cephalad spread

Mean cephalad spread of analgesia was T7.5 in both groups. Maximal extent of analgesia was T3 in group 1 and T4 in group 2. Analgesia above T6 was reached by 5/20 in group 1 and 6/20 in group 2. There were no significant differences between the groups (fig. 1).

Onset time

Onset time to T12 level was 7.8 and 8.5 min and onset to T10 level was 9.7 and 10.5 min in the 3-ml (group 1) and 6-ml (group 2) groups, respectively ($P > 0.05$). Maximal extension of analgesia was reached in 26 min in the 3-ml group and, insignificantly faster, in 21 min in the 6-ml group. However, some patients exhibited a maximum cephalad spread in 5 min, others in 60 min, independent of the volume used.

Duration of analgesia

Approximate duration of analgesia above T12 was 165 min, and above T10, 100 min. There was no significant difference between the two groups (table II).

Motor blockade

All patient experienced degree 3 blockade. Mean onset time to degrees 2 and 3 is shown in

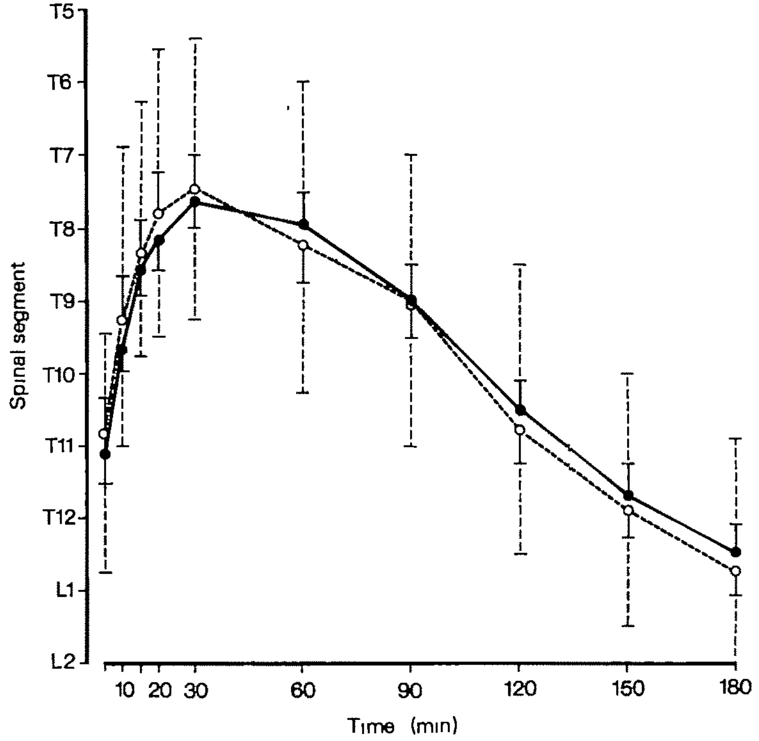

FIG. 1. Spread of analgesia after intrathecal injection of plain bupivacaine 15 mg. Solid vertical bars represent SEM, dotted vertical lines represent SD. ○.....○ = 0.25% plain bupivacaine 6 ml. ●——● = 0.50% plain bupivacaine 3 ml.

TABLE II. *Duration of analgesia (mean (SD))*

	0.5 % Bupivacaine 3 ml		0.25 % Bupivacaine 6 ml	
Analgesia	*n*	Duration (min)	*n*	Duration (min)
> T12	20/20	165 (48.8)	20/20	163 (43.5)
> T10	19/20	115 (52.0)	19/20	109 (45.7)
> T8	13/20	75 (37.9)	10/20	91 (34.8)

TABLE III. *Onset time (min) of motor blockade (mean (SD))*

	0.5 % Bupivacaine 3 ml	0.25 % Bupivacaine 6 ml
To degree 2	8.9 (3.9)	10.3 (7.5)
To degree 3	14.2 (5.8)	17.3 (12.6)

table III. Complete paralysis was seen after 20 min in all patients except one in each group. Duration of total motor blockade was approximately 175 min in both groups. Regression of blockade was not complete in all patients until 6.5 h after injection. Duration of sensory block with simultaneous total motor blockade lasted approximately 2.5 h at T12, 1.6 h at T10 and 1.2 h at T8. The differences between the groups were small and not significant (table IV).

Cardiovascular effects

The decrease in mean systolic arterial pressure was minimal, and there was no significant difference in heart rate between the groups. Two patients in each group received ephedrine 10 mg i.v.

DISCUSSION

Earlier studies on the effects of change in volume, concentration and dose of plain bupivacaine have investigated only 0.5 % and 0.75 % solutions. By comparing the effects of bupivacaine 15 mg given as 0.25 % and 0.5 % solutions, we created a difference in volume of 100 %, which is considerably greater than in former studies, and investigated the use of a 0.25 % solution of plain bupivacaine for spinal anaesthesia.

Onset time, duration and spread of analgesia in the present study are comparable to the results of an earlier study using 15 mg of plain 0.5 % or 0.75 % bupivacaine [4], although an insignificantly longer duration and shorter onset time were observed with the more concentrated solution. In a study using bupivacaine 22.5 mg, no differences were noticed between volumes of 3 or 4.5 ml, although onset time was shorter and duration longer than in our groups, probably because of difference in total dose [11].

We found no differences in any of the variables investigated when comparing 0.5 % bupivacaine 3 ml with 0.25 % bupivacaine 6 ml. This is not in accord with the conclusions of Logan, McClure and Wildsmith [6], who claimed that a larger volume would produce a greater displacement of CSF and contribute to the unpredictability of spinal analgesia with plain bupivacaine. However, the two studies examined different doses, concentrations and positioning of the patient.

Motor blockade was total in both our groups and onset was insignificantly faster in group 1. Duration of total paralysis and time to total resolution of blockade were independent of the concentration used. The cardiovascular effects were small and the degree of hypotension and change in heart rate were similar in both groups.

As has been noted [9], local anaesthetics should not be used in higher concentrations than is

TABLE IV. *Duration of analgesia with simultaneous total motor blockade (mean (SD))*

	0.5 % Bupivacaine 3 ml		0.25 % Bupivacaine 6 ml	
Analgesia	*n*	Duration (min)	*n*	Duration (min)
> T12	20/20	149 (49.1)	20/20	142 (43.3)
> T10	19/20	107 (51.8)	19/20	99 (44.3)
> T8	10/20	70 (35.2)	10/20	82 (42.2)

indicated clinically, because of the possible neurotoxicity of bupivacaine. In this respect the 0.25% solution may be preferable to the 0.75% and 0.5% solutions.

In conclusion, we found no differences in onset time, spread and duration of analgesia or in quality of motor blockade when plain 0.5% bupivacaine 3 ml was compared with plain 0.25% bupivacaine 6 ml.

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Br. J. Anaesth. (1989), **62**, 168–176

RELATIONSHIP BETWEEN ALVEOLAR DEADSPACE AND ARTERIAL OXYGENATION IN CHILDREN WITH CONGENITAL CARDIAC DISEASE†

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SUMMARY

Fifty-eight children were studied during nitrous oxide in oxygen and fentanyl anaesthesia before undergoing closed or open cardiac surgery. $F_{I_{O_2}}$ *was 0.5. Alveolar deadspace was measured using the carbon dioxide single breath test (SBT-CO_2) obtained from a computerized on-line system for monitoring expired CO_2 and airway flow, based on the Servo ventilator. Arterial blood was sampled simultaneously for measurement of* Pa_{CO_2} *and* Pa_{O_2}*. There was a marked reciprocal relationship between* Pa_{O_2} *and the alveolar deadspace fraction. In children with a normal pulmonary circulation and good oxygenation, alveolar deadspace fraction was approx. 0.05. Shunts which reduced* Pa_{O_2} *to 10 kPa produced a deadspace fraction of 0.15. When* Pa_{O_2} *was 3–4 kPa, alveolar deadspace fraction was approx. 0.4. In well-oxygenated children, alveolar deadspace fraction was only slightly greater than predicted by a model of the effects of pure right-to-left shunting. In severely cyanotic children, the discrepancy between predicted and observed* V_D^{alv}/V_T^{alv} *was greater. The mean arterial–end-tidal CO_2 difference was zero in children in whom* Pa_{O_2} *was greater than 10 kPa, despite a measurable alveolar deadspace. In severely hypoxic children, the difference was 1–2 kPa. In a retrospective analysis of published data from anaesthetized adults without intracardiac shunting, no relationship was found between alveolar deadspace and* Pa_{O_2}*.*

Intracardiac right-to-left (RL) shunts produce differences between alveolar and arterial partial pressures for oxygen and carbon dioxide. The alveolar–arterial differences in $P\text{CO}_2$ are deliberately ignored in the conventional calculation of the shunt fraction $\dot{Q}s/\dot{Q}t$. The calculation is based on the contents of oxygen in arterial, mixed venous and pulmonary end-capillary blood (Ca_{O_2}, $C\bar{v}_{O_2}$ and Cc_{O_2}, respectively):

$$\frac{\dot{Q}s}{\dot{Q}t}=\frac{(Cc_{O_2}-Ca_{O_2})}{(Cc_{O_2}-C\bar{v}_{O_2})} \tag{1}$$

Cc_{O_2} is estimated from the haemoglobin dissociation curve and Pc_{O_2}, the $P\text{O}_2$ of pulmonary end-capillary blood; the latter is estimated from the ideal alveolar gas equation:

$$Pc_{O_2}=PA_{O_2}=PI_{O_2}-\frac{PA_{CO_2}}{R} \tag{2}$$

where PA_{O_2} and PA_{CO_2} are the ideal alveolar partial pressures of oxygen and carbon dioxide; R = respiratory quotient; PI_{O_2} = inspired partial pressure of oxygen. PA_{CO_2} is assumed to be equal to Pa_{CO_2} (the arterial $P\text{CO}_2$), although for any appreciable $\dot{Q}s/\dot{Q}t$ this cannot be true. However, the assumption can give only a small error in the estimate of PA_{O_2}; if PA_{O_2} is increased by a sufficiently increased PI_{O_2}, end-capillary haemoglobin is fully saturated and the resulting error in the estimate of Cc_{O_2} is negligible. The dissolved oxygen, the only component which can be affected by the error, makes only a small contribution to total Cc_{O_2}.

However, for any appreciable $\dot{Q}s/\dot{Q}t$, there is an appreciable alveolar–arterial $P\text{CO}_2$ difference. Although it results from a circulatory disturbance, a RL shunt reduces the efficiency of elimination of carbon dioxide. This effect can be expressed as a

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contribution to the *alveolar deadspace fraction* of alveolar tidal volume:

$$\frac{V\text{D}^{\text{alv}}}{V\text{T}^{\text{alv}}} = \frac{P\text{a}_{\text{CO}_2} - P\text{A}_{\text{CO}_2}}{P\text{a}_{\text{CO}_2} - P\text{I}_{\text{CO}_2}} \tag{3}$$

or, if $P\text{I}_{\text{CO}_2}$ is zero:

$$\frac{V\text{D}^{\text{alv}}}{V\text{T}^{\text{alv}}} = 1 - \frac{P\text{A}_{\text{CO}_2}}{P\text{a}_{\text{CO}_2}} \tag{4}$$

In a real lung, the alveolar gas is inhomogeneous. $P\text{A}_{\text{CO}_2}$ cannot, therefore, be represented by the $P\text{CO}_2$ of gas sampled in any selected part of the alveolar space, or any instant in time (for example, end-tidal $P\text{CO}_2$, $P\text{E}'_{\text{CO}_2}$); and it is not necessarily represented by the mean $P\text{CO}_2$ of the alveolar part of the expired tidal volume, $P\overline{\text{AE}}_{\text{CO}_2}$. Nevertheless, if $P\overline{\text{AE}}_{\text{CO}_2}$ is used in equation (3) instead of $P\text{A}_{\text{CO}_2}$, one does obtain a useful measure of inefficiency of elimination of carbon dioxide:

$$\frac{V\text{D}^{\text{alv}}}{V\text{T}^{\text{alv}}} = 1 - \frac{P\overline{\text{AE}}_{\text{CO}_2}}{P\text{a}_{\text{CO}_2}} \tag{5}$$

The average concentration of any gas in the alveolar portion of the expirate can be measured by use of single breath analysis. This concept, introduced by Aitken and Clarke-Kennedy [1] and re-iterated later by Fowler [2], has been developed [3–6] as a computerized on-line technique for monitoring carbon dioxide elimination during ventilator treatment. It is used routinely in this department during paediatric cardiac anaesthesia. The single breath test for carbon dioxide (SBT-CO_2), is obtained by combining signals for airway flow and expired carbon dioxide, both of which are becoming recognized as desirable facets of routine monitoring.

This paper describes the use of SBT-CO_2 to estimate $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ in a group of children about to undergo cardiac surgery. Many of the children were cyanotic, with right-to-left (RL) or mixed RL and left-to-right (LR) shunts. The paper examines particularly the inverse relationship between $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ and $P\text{a}_{\text{O}_2}$ which was found in these children; this contrasts with the lack of relationship seen in a group of adults studied in a similar way (unpublished data from Fletcher and Jonson [3]). The observations are compared with the results of a theoretical model of the $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ *v.* $P\text{a}_{\text{O}_2}$ relationship which should follow from pure RL shunting.

THEORY

Relationship between $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ *and* $P\text{a}_{\text{O}_2}$ *for different RL shunts*

For a pure RL shunt, $\dot{Q}\text{s}/\dot{Q}\text{t}$ is related to the oxygen contents $C\text{a}_{\text{O}_2}$, $C\bar{\text{v}}_{\text{O}_2}$ and $C\text{c}_{\text{O}_2}$ by equation (1). This principle can be applied equally to carbon dioxide contents:

$$\frac{\dot{Q}\text{s}}{\dot{Q}\text{t}} = \frac{(C\text{a}_{\text{CO}_2} - C\text{c}_{\text{CO}_2})}{(C\bar{\text{v}}_{\text{CO}_2} - C\text{c}_{\text{CO}_2}} \tag{6}$$

Rearranging equations (1) and (6), it can be shown that, for a given $\dot{Q}\text{s}/\dot{Q}\text{t}$, the arterial–end-capillary differences can be calculated from arteriovenous differences:

$$(1 - \dot{Q}\text{s}/\dot{Q}\text{t}).(C\text{c}_{\text{O}_2} - C\text{a}_{\text{O}_2}) = \dot{Q}\text{s}/\dot{Q}\text{t}.(C\text{a}_{\text{O}_2} - C\bar{\text{v}}_{\text{O}_2}) \tag{7}$$

and

$$(1 - \dot{Q}\text{s}/\dot{Q}\text{t}).(C\text{a}_{\text{CO}_2} - C\text{c}_{\text{CO}_2}) = \dot{Q}\text{s}/\dot{Q}\text{t}.(C\bar{\text{v}}_{\text{CO}_2} - C\text{a}_{\text{CO}_2}) \tag{8}$$

Thus the expected arterial–end-capillary differences can be calculated from arteriovenous differences for a given shunt. Dividing equation (8) by equation (7), it also follows that the respiratory quotient R describes, not only the ratio of arteriovenous differences in carbon dioxide and oxygen contents, but also the ratio of end-capillary–arterial and end-capillary–mixed venous differences. Thus:

$$\frac{(C\text{a}_{\text{CO}_2} - C\text{c}_{\text{CO}_2})}{(C\text{c}_{\text{O}_2} - C\text{a}_{\text{O}_2})} = R \tag{9}$$

If ventilation is controlled to maintain a constant $P\text{a}_{\text{CO}_2}$, and if $F\text{I}_{\text{O}_2}$ is increased to 0.4 or more, $C\text{a}_{\text{CO}_2}$ and $C\text{c}_{\text{O}_2}$ will be fixed. $C\text{c}_{\text{CO}_2}$ and $C\text{a}_{\text{O}_2}$ will vary with $\dot{Q}\text{s}/\dot{Q}\text{t}$. The corresponding $P\text{A}_{\text{CO}_2}$ and $P\text{a}_{\text{O}_2}$ can be determined by applying the appropriate oxygen and carbon dioxide dissociation curves for blood of appropriate haemoglobin content. Finally, $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ can be calculated from equation (3) and plotted against $P\text{a}_{\text{O}_2}$ to give the theoretical relationship between the two variables. If the oxygen and carbon dioxide dissociation curves were simple linear relationships, the $P\text{a}_{\text{O}_2}$ *v.* alveolar deadspace fraction relationship would also be linear. The non-linearity of the Hb dissociation curve is reflected in the non-linearity of the $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ *v.* $P\text{a}_{\text{O}_2}$ relationship.

There are several possible contributions to the V_D^{alv}/V_T^{alv} *v.* Pa_{O_2} relationship, in addition to that of a pure RL shunt (see discussion). This paper attempts to assess their importance by comparing the theoretical relationship with observations in children with cyanotic and acyanotic heart disease.

PATIENTS AND METHODS

Fifty-eight children about to undergo closed or open cardiac surgery were studied in the supine position during undisturbed fentanyl–nitrous oxide anaesthesia with intermittent positive pressure ventilation (IPPV). Eight of the children also received 0.5% halothane. $F_{I_{O_2}}$ was 0.50. The ventilator, a Servo 900C, was set to give constant-flow, volume-controlled ventilation at a frequency of 25–35 b.p.m., depending on body weight, and an inspiratory time of 25% with 10% pause. Minute volume was adjusted to give moderate hypocapnia (Pa_{CO_2} 4–5 kPa). Positive end-expiratory pressure was not used.

The children (some of whose deadspace values have been described previously [6]) were allocated to four groups according to the characteristics of their central circulation, determined by preoperative angiography, intracardiac pressure and saturation measurements, echocardiography, chest x-ray and haemoglobin determinations. Thus 13 were shown to have normal lungs and pulmonary circulation, 17 had pure left-to-right (LR) intracardiac shunting, 18 had pure RL shunting and 10 probably had mixed RL–LR shunting. Diagnoses, anthropomorphic details and some gas exchange variables are given in tables I and II.

Measurements were made using an on-line system for monitoring expired carbon dioxide [7]. A Facit computer received signals for airway flow and pressure from the ventilator, and signals for expired P_{CO_2} from a Siemens–Elema CO_2 Analyzer 930 [8]. As the transducer of the carbon dioxide analyser is placed directly across the airway ("in-line") there is no sampling lag and consequently, airway flow and carbon dioxide signals are virtually synchronous [5]. The com-

TABLE I. *Diagnoses in the children. ASD, VSD = atrial, ventricular septal defects; PDA = patent ductus arteriosus; TGA = transposition of the great arteries; AVC = common atrioventricular canal; TAPV = total anomalous pulmonary venous drainage*

Normal circulation		LR shunts		RL shunts		Mixed shunts	
Pulmonary stenosis	3	ASD	6	TGA	5	"Acyanotic Fallot"	4
Aortic coarctation	2	VSD	3	Pulmonary stenosis or atresia	9	TGA	1
Aortic stenosis	3	Large PDA	8			TAPV, ASD	1
Small PDA	5	Total	17			VSD, pulmonary hypertension	2
Total	13			Fallot's tetralogy	4	AVC	2
				Total	18	Total	10

TABLE II. *Ages, weights and some ventilatory variables in the children (mean (SD or range)). Significantly different from group with normal circulation, after Bonferroni correction*: $^{**}P < 0.01$; $^{*}P = 0.05$

	Age (yr)	Weight (kg)	V_T (ml)	Pa_{O_2} (kPa)	$\frac{V_D^{alv}}{V_T^{alv}}$	$(Pa_{CO_2} - P_{E'_{CO_2}})$ (kPa)
Normal pulmonary circulation ($n = 13$)	5.5 (3.7)	19.8 (9.1)	170 (69)	33.8 (5.5)	0.05 (0.03)	0.0 (0.1)
LR shunt ($n = 17$)	3.6 (3.0)	13.7 (6.9)	119 (44)	26.8 (6.2)**	0.05 (0.05)	0.0 (0.2)
RL shunt ($n = 18$)	2.4 (2.0)**	9.2 (5.3)**	79 (38)**	7.3 (2.5)**	0.25 (0.12)**	1.0 (0.3–2.0)**
Mixed shunt ($n = 10$)	1.3 (1.3)**	8.8 (4.0)**	80 (31)**	13.2 (1.3)**	0.12 (0.07)	0.3 (−0.2–0.8)*

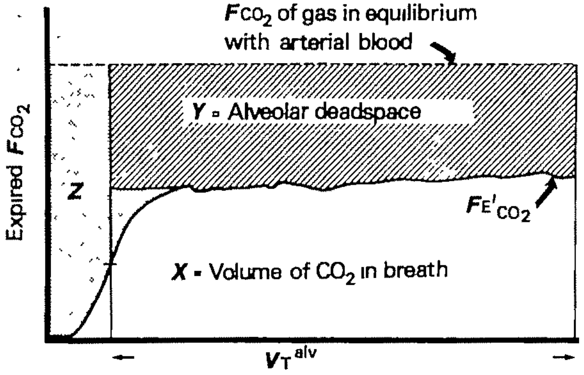

FIG. 1. Typical carbon dioxide single breath test from a child with a large RL shunt. Area Z represents the airway deadspace. $V\mathrm{D}^{\mathrm{alv}}/V\mathrm{T}^{\mathrm{alv}}$ can be represented by $Y/(X+Y)$.

puter presented the single breath test for carbon dioxide (SBT-$\mathrm{CO_2}$) (the plot of expired carbon dioxide against expired volume) and calculated deadspace from a supplied value for $P\mathrm{a}_{\mathrm{CO_2}}$.

Figure 1 shows a typical single breath test from a child with a large RL shunt. The shape of the curve can be described as follows: the initial expirate has zero carbon dioxide content (phase I). Thereafter follows a sharp increase in $F\mathrm{E}_{\mathrm{CO_2}}$ (phase II) as alveolar gas begins to reach the airway opening. Phase III is sometimes referred to as the alveolar plateau. It consists of alveolar gas, and normally has a slight slope, caused by (a) the continuing output of carbon dioxide into the alveoli, and (b) spread of ventilation/perfusion ($\dot{V}/\dot{Q}$) values; areas of high $\dot{V}/\dot{Q}$ normally empty before those of low $\dot{V}/\dot{Q}$ [4]. The contribution of (a) to phase III slope during mechanical ventilation in children can be shown to be small [4].

The area under the curve is the volume of carbon dioxide in the breath, $V\mathrm{T}_{\mathrm{CO_2}}$. The airway deadspace, $V\mathrm{D}^{\mathrm{aw}}$, was obtained as the volume of the expirate when $F\mathrm{E}_{\mathrm{CO_2}}$ was 50% of early phase III $F\mathrm{CO_2}$. (This construction is feasible only in children, in whom phase III slope is small.) Physiological deadspace was obtained from:

$$V\mathrm{D}^{\mathrm{phys}}/V\mathrm{T} = \frac{F\mathrm{a}_{\mathrm{CO_2}} - F\bar{\mathrm{E}}_{\mathrm{CO_2}}}{F\mathrm{a}_{\mathrm{CO_2}} - F\mathrm{I}_{\mathrm{CO_2}}} \qquad (10)$$

where $F\bar{\mathrm{E}}_{\mathrm{CO_2}}$, mixed expired $F\mathrm{CO_2}$, was obtained from $V\mathrm{T}_{\mathrm{CO_2}}/V\mathrm{T}$. Inspired $F\mathrm{CO_2}$ ($F\mathrm{I}_{\mathrm{CO_2}}$) is not zero because approximately 3 ml of apparatus deadspace gas is inspired from the Y-piece. $F\mathrm{I}_{\mathrm{CO_2}}$ was estimated by dividing the carbon dioxide content of this gas (regarded as being end-tidal gas) by the alveolar tidal volume ($V\mathrm{T}^{\mathrm{alv}}$) which is given by ($V\mathrm{T} - V\mathrm{D}^{\mathrm{aw}}$). $F\mathrm{a}_{\mathrm{CO_2}}$, the $F\mathrm{CO_2}$ of a gas in equilibrium with arterial blood, was calculated by the computer from a temperature-corrected value for $P\mathrm{a}_{\mathrm{CO_2}}$. Body temperature was measured by an oesophageal probe. $V\mathrm{D}^{\mathrm{alv}}$ was obtained from ($V\mathrm{D}^{\mathrm{phys}} - V\mathrm{D}^{\mathrm{aw}}$). The slope of phase III was measured as the increase in $F\mathrm{E}_{\mathrm{CO_2}}$ between expired volumes of 5% and 10% of predicted total lung capacity, divided by the mean $F\mathrm{E}_{\mathrm{CO_2}}$ between these points.

Data from adults for comparison were taken from the patients presented by Fletcher and Jonson [3]. That study examined $V\mathrm{D}^{\mathrm{alv}}/V\mathrm{T}^{\mathrm{alv}}$ and several different variables, although not $P\mathrm{a}_{\mathrm{O_2}}$.

Deadspace variables were obtained as the mean of three breaths, sampled at the same time as arterial blood for blood-gas analysis (ABL2; Radiometer, Copenhagen) was withdrawn slowly from an indwelling femoral or radial artery catheter. (None of the children had RL shunting through a patent ductus arteriosus, therefore choice of sampling site should not influence the $P\mathrm{a}_{\mathrm{O_2}}$ obtained.) The carbon dioxide analyser was calibrated daily against a test gas which had been checked by tonometry against the blood-gas analyser. Blood-gas values were corrected to body temperature, according to Kelman and Nunn [9]. Deadspace variables were corrected for a tidal volume-dependent error in carbon dioxide measurement [6].

Student's t test was used for statistical comparisons. For the multiple comparisons in table I, the Bonferroni correction was applied.

Predicted alveolar deadspace–$P\mathrm{a}_{\mathrm{O_2}}$ relationship

In order to compare the observations with those that could be expected if RL shunting were the sole cause of alveolar deadspace, a model was constructed. The approach described in the theory section (above) was applied. $V\mathrm{D}^{\mathrm{alv}}/V\mathrm{T}^{\mathrm{alv}}$ and $P\mathrm{a}_{\mathrm{O_2}}$ were calculated for nine different values of $\dot{Q}\mathrm{s}/\dot{Q}\mathrm{t}$ (fig. 2) assuming:

$F\mathrm{I}_{\mathrm{O_2}} = 0.5$

Hb concentration = 16 g dl^{-1} (representing a mean value for all the children)

Oxygen combining capacity = 1.34 ml g^{-1}

The oxyhaemoglobin dissociation curve of Kelman and Nunn [9]

The carbon dioxide dissociation curve given by Nunn [10]

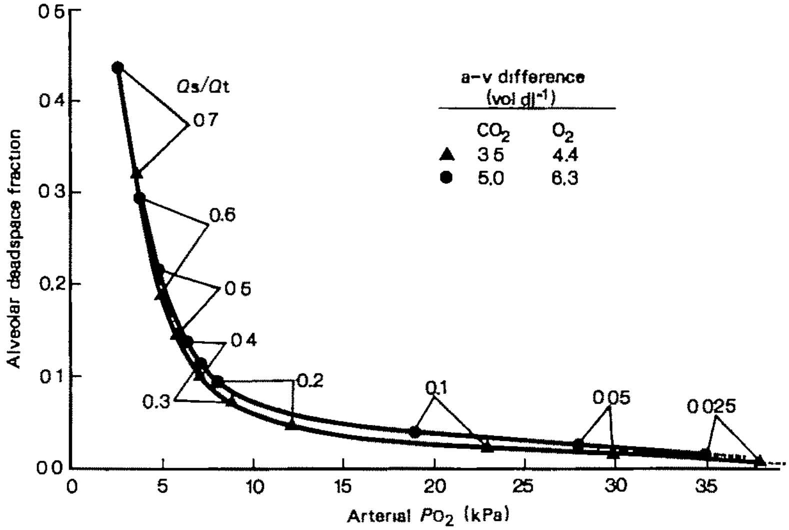

FIG. 2. Predicted relationship between Pa_{O_2} and $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$: expected values at different shunt fractions and two different arteriovenous differences, compatible with a respiratory quotient of 0.8.

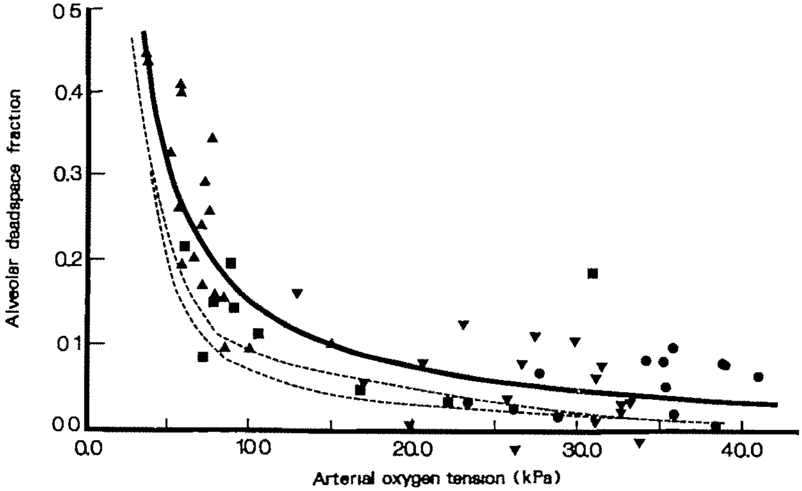

FIG. 3. Relationship between Pa_{O_2} and alveolar deadspace fraction. Children with normal pulmonry circulation (●); LR shunting (▼); RL shunting (▲); mixed shunting (■). The dotted lines show the prediction illustrated in figure 2.

Normal pH and temperature

An RQ of 0.8

Two different values of arteriovenous difference in oxygen content: 4.4 and 6.3 ml dl^{-1}.

Linear regression of the predicted values for $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ against $1/Pa_{O_2}$ (kPa) gave the following:

$V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}} = 1.10/Pa_{O_2} - 0.030$;
$r = 0.98$ for the lesser $(\text{a}-\bar{\text{v}})$ difference;
$V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}} = 1.22/Pa_{O_2} - 0.028$;
$r = 0.99$ for the greater $(\text{a}-\bar{\text{v}})$ difference (fig. 2).

RESULTS

Children

There was an inverse relationship between $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ and temperature-corrected Pa_{O_2} (kPa), described by the regression equation:

$V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}} = -0.007 + 1.607/Pa_{O_2}$;
$r = 0.87$; residual standard deviation (RSD) = 0.059.

The observations and the regression lines (solid line) are plotted in figure 3. For comparison, the

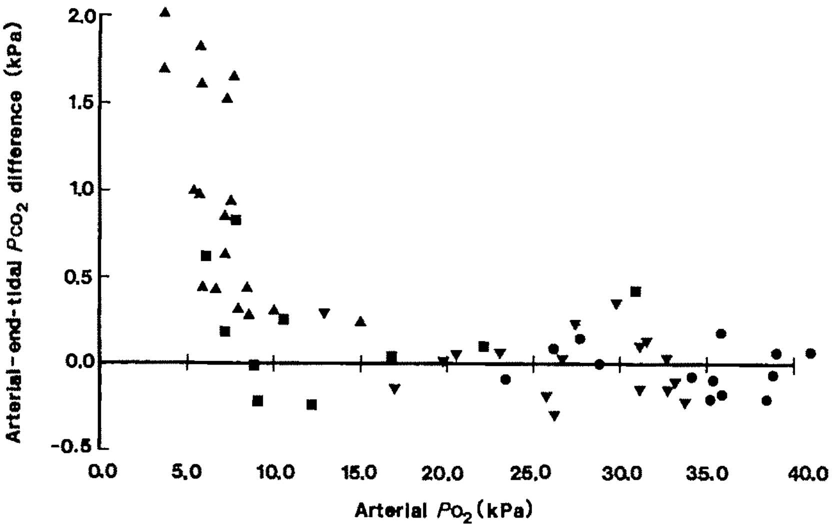

FIG. 4. Relationship between Pa_{O_2} and the arterial–end-tidal P_{CO_2} difference. Children with normal pulmonary circulation (●); LR shunting (▼); RL shunting (▲); mixed shunting (■).

figure also shows the relationship (broken lines) predicted by the theoretical model (fig. 2) for the two $(a-\bar{v})$ oxygen differences. There were significant correlations between $1/Pa_{O_2}$ and VD^{alv}/VT^{alv} in the LR and RL groups:

LR: $VD^{alv}/VT^{alv} = 0.023 + 1.97/Pa_{O_2}$;
$r = 0.49$, $P = 0.05$
RL: $VD^{alv}/VT^{alv} = 0.023 + 1.79/Pa_{O_2}$;
$r = 0.81$, $P = 0.0001$

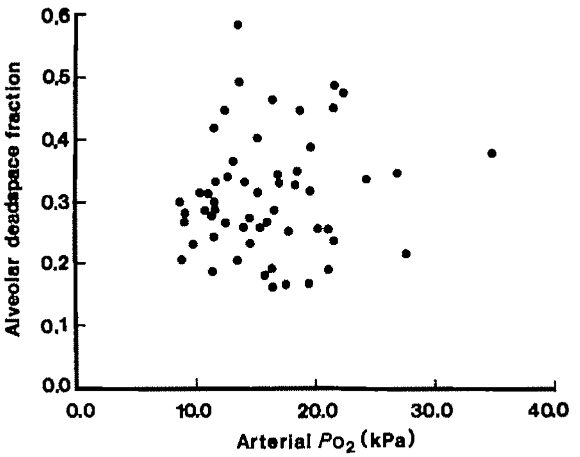

FIG. 5. Relationship between Pa_{O_2} and alveolar deadspace fraction in adults. Results from the patients presented by Fletcher and Jonson [3].

In the normal circulation ($r = -0.35$) and mixed shunt groups ($r = 0.44$) the correlations were not significant. Pa_{O_2} correlated positively with age in the children with normal circulation and those with LR shunts ($r = 0.38$, $P = 0.04$).

In the well-oxygenated children (LR and normal circulation groups), but not the others, the slope of phase III of SBT-CO$_2$ correlated negatively with Pa_{O_2} ($r = -0.36$, $P = 0.04$). The relationship between Pa_{O_2} and the arterial–end-tidal P_{CO_2} difference ($Pa_{CO_2} - P{E'}_{CO_2}$) is shown in figure 4.

Adults

Results from the adults are shown in figure 5. FI_{O_2} was 0.35. There was no relationship between VD^{alv}/VT^{alv} and Pa_{O_2} ($r = 0.13$, $P = 0.3$), or $1/Pa_{O_2}$ ($r = -0.14$, $P = 0.3$).

DISCUSSION

The alveolar deadspace fraction of alveolar tidal volume (VD^{alv}/VT^{alv}) is a notional representation of imperfections in pulmonary gas exchange which create a difference between $P\overline{AE}_{CO_2}$ and Pa_{CO_2}, by decreasing the former or increasing the latter, or both. Pa_{CO_2} is measured readily in a sample of arterial blood, but it is necessary to use SBT-CO$_2$ to measure $P\overline{AE}_{CO_2}$ because no single sample of alveolar expirate can represent the mean

$P\text{CO}_2$ of alveolar expirate. SBT-CO_2 has been shown to measure expired carbon dioxide accurately during controlled ventilation [11], although it is necessary to correct for a small systematic error which occurs at tidal volumes of less than 200 ml [6].

The concept of alveolar deadspace is regarded usually as representing wasted or inefficient ventilation, caused by ventilation of poorly- or non-perfused alveoli. The primary effect of this is to reduce $P\text{A}_{\text{CO}_2}$ and therefore to increase alveolar deadspace, with no obligatory effect on Pa_{O_2}. However, circulatory inefficiency, such as intracardiac RL shunting or perfusion of poorly- or non-ventilated areas (with low or zero ventilation/perfusion ($\dot{V}/\dot{Q}$) ratios), also produces a measurable alveolar deadspace (which does not, however, represent ventilation of any compartment). Such circulatory inefficiency increases Pa_{CO_2} and reduces Pa_{O_2}.

The primary effect of ventilatory inefficiency is thus to increase $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ with no obligatory effect on Pa_{O_2}, whereas circulatory inefficiency affects both $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ and Pa_{O_2}. These primary effects may be accompanied by secondary effects from disturbances in $\dot{V}/\dot{Q}$ distribution; if, for instance, ventilation is diverted to deadspace, some regions of low $\dot{V}/\dot{Q}$ may be created. Similarly, if perfusion is diverted to a RL shunt, some regions of high $\dot{V}/\dot{Q}$ (pulmonary hypoperfusion) may occur. The general effect of secondary effects is to add to the $Pa_{\text{CO}_2}-P\text{A}_{\text{CO}_2}$ difference created by primary defects, and this may be accompanied by some reduction in Pa_{O_2} (see below).

The occurrence of secondary effects depends on whether or not the ventilatory and circulatory inefficiencies are accompanied by overall respective increases in $\dot{V}$ or $\dot{Q}$. If there is deadspace ventilation, a compensatory increase in overall ventilation can prevent the secondary creation of low $\dot{V}/\dot{Q}$ regions. Similarly, in RL shunting, a compensatory increase in total $\dot{Q}$ may prevent the appearance of regions of high $\dot{V}/\dot{Q}$.

The children with RL shunts were younger and weighed less than those with normal circulation. Cyanotic children usually require surgery at an earlier age than those with non-cyanotic lesions, and it is difficult to see how this age difference can be avoided in a clinical investigation. The smaller children may have a greater tendency to atelectasis [12], and in the present study, Pa_{O_2} increased with age in the acyanotic children. However, this should not greatly affect the results, as any reduction in Pa_{O_2} produced by RL shunting via atelectasis should be accompanied by an increase in alveolar deadspace.

The shape of the observed $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ *v.* Pa_{O_2} curve in children agrees well with the prediction (figs 2 and 3). The curve is approximately hyperbolic because the oxyhaemoglobin dissociation curve, which relates oxygen tension to content, is also approximately hyperbolic. (If $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ is plotted against oxygen saturation (or content), a straight line is obtained (Fletcher, unpublished results)). However, compared with the prediction, the observed $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ *v.* Pa_{O_2} curve is displaced upwards by approximately 0.04 at Pa_{O_2} 33.8 kPa (the mean value of the normal group), and by 0.07–0.08 at 7.3 kPa (RL group mean). At 5 kPa, the discrepancy increases further to approximately 0.10.

In the well-oxygenated children, the discrepancy between observed and expected $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ is small; some of it may result from systematic error which is produced when the Siemens–Elema 930 CO_2 Analyzer is used at paediatric tidal volumes. This arises because the zero calibration is reset during each inspiration, when the transducer is flushed with fresh gas. Small tidal volumes fail to remove carbon dioxide completely. Because the new zero is established before the (logarithmic) carbon dioxide signal is linearized, carbon dioxide molecules remaining in the transducer at this stage have a disproportionately great effect. The zero error reduces the measured $P\text{CO}_2$ of the next expiration. Correction factors, obtained from two large series of observations [6], have been applied to $V\text{T}_{\text{CO}_2}$ and $F\text{E}'_{\text{CO}_2}$. If this factor should prove to be too small, values for $V\text{D}^{\text{alv}}$ in this study will have been systematically overestimated. In well oxygenated children, a 1% error in measurement of $P\text{A}_{\text{CO}_2}$ or Pa_{CO_2} gives an error of 0.01 in $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$; in the cyanotic children, the effect is less.

Calculation of deadspace in the children (equation (10)) included insertion of a value for $F\text{I}_{\text{CO}_2}$, arising from carbon dioxide rebreathed in the Y-piece. The effect of this on $V\text{D}^{\text{alv}}$ is less than 0.01, even in the smallest children. Other reasons for the discrepancy between observed and predicted $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ may be temporal deadspace or imperfect gas mixing. Temporal deadspace implies temporal mismatching of ventilation and perfusion. This may occur during positive pressure ventilation; pulmonary blood flow is maximal at end-expiration, when ventilation is least. Some small degree of imperfect gas mixing cannot be ruled out, as even normal children have a slightly positive phase III slope. Finally, there is the possibility of secondary effects of ventilatory and, probably more importantly, circulatory inefficiency (see below).

In the children with RL shunts there is a very strong $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ *v.* Pa_{O_2} relationship, as the model predicts. RL shunts are often regarded as causing "pulmonary hypoperfusion"—that is, inadequate pulmonary circulation giving rise to $\dot{V}/\dot{Q}$ ratios greater than optimal. Such pulmonary hypoperfusion was discussed above as being a secondary effect of circulatory inefficiency. There is some evidence for hypoperfusion in the present observations, as the discrepancy between observed and expected $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ in these children increases somewhat with decreasing Pa_{O_2}. However, cyanotic children have an increased cardiac output, and so areas of increased $\dot{V}/\dot{Q}$ may perhaps be created only when the shunt is extremely large; for instance, a child with a shunt of 0.3 (Pa_{O_2} 7–8 kPa) would have a normal pulmonary blood flow if its cardiac output was increased to 143 % of normal. However, in order to confirm the existence of such secondary effects, it is necessary to compare pulmonary vein blood and alveolar gas carbon dioxide tensions in severely cyanotic children; this has not yet been done.

As a rule, children with LR shunting have excellent gas exchange. They differ from those with normal circulation only in having a slightly reduced Pa_{O_2} and an increased phase III slope, these variables being negatively correlated with each other. An increased phase III slope implies increased $\dot{V}/\dot{Q}$ spread, which in turn implies an increase in $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$. However, it is not possible to demonstrate any such increase in the present material; it is probably of too small a magnitude. Pulmonary artery $P\text{O}_2$ is increased in these children and, therefore, perfusion of low or zero $\dot{V}/\dot{Q}$ areas does not affect Pa_{O_2} to the same extent as in normal children. Furthermore, perfusion of low $\dot{V}/\dot{Q}$ areas does not necessarily imply underperfusion of other areas, and therefore secondary effects are probably unimportant.

Much of the alveolar deadspace demonstrated in these children with congenital cardiac disease may thus be explained by RL shunting. The residual deadspace may result from several factors, including a possible systematic measurement error, temporal deadspace, and deadspace produced by imperfect gas mixing in the lung. In children with severe cyanotic disease, deadspace may be created also by secondary effects of the RL shunt—that is, failure of perfusion of the lung parenchyma.

The arterial–end-tidal carbon dioxide difference shows a relationship to Pa_{O_2} which is approximately similar to that of $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$. However, $(Pa_{CO_2} - P\text{E}'_{CO_2})$ is approximately zero for all Pa_{O_2} values of 10 kPa and greater, whereas $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ is approximately 0.15 at 10 kPa. The reason for this is that, as stated above, in the range of Pa_{O_2} greater than 10 kPa, phase III slope increases with decreasing Pa_{O_2}, these two features being associated with increased pulmonary perfusion. A sloping phase III allows a zero arterial–end-tidal carbon dioxide difference, even when the alveolar deadspace is increased. This is seen occasionally in healthy adults undergoing ventilation with large tidal volumes [3].

Finally, figure 5 shows that there is no relationship between alveolar deadspace and oxygenation during anaesthesia in an adult general surgical population. This suggests that much of the alveolar deadspace is produced by primary ventilatory inefficiencies. There are probably also secondary effects. In general, increased alveolar deadspace in adults is the result of airways disease, which causes an increased spread of $\dot{V}/\dot{Q}$ ratios and an increase in phase III slope. Phase III slope in a middle-aged individual is usually much steeper than that seen in children.

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PHARMACOKINETICS OF ATRACURIUM AND LAUDANOSINE IN PATIENTS WITH HEPATIC CIRRHOSIS

C. J. R. PARKER AND J. M. HUNTER

SUMMARY

The pharmacokinetic profiles of atracurium and one of its derivatives, laudanosine were studied following an i.v. bolus of atracurium 0.6 mg kg^{-1} *administered to eight patients with hepatic cirrhosis and to seven healthy controls. The central volume of distribution of atracurium was greater in the patients with cirrhosis (104.6 ml* kg^{-1}*) compared with the controls (89.6 ml* kg^{-1}*) (*$P < 0.05$*), as was the total volume of distribution (281.8 ml* kg^{-1} *and 202.1 ml* kg^{-1}*, respectively) (*$P < 0.05$*). There was no significant difference in the elimination half-life of atracurium between the two groups. The total volume of distribution of laudanosine was increased in cirrhotic patients (2.68 litre* kg^{-1}*) compared with healthy controls (1.97 litre* kg^{-1}*) (*$P < 0.05$*). as was its elimination half-life (277 min in cirrhotic individuals; 168 min in controls) (*$P < 0.05$*). There was no significant difference in the clearance of laudanosine between the two groups.*

Patients with hepatic cirrhosis are known to be resistant to the action of several non-depolarizing neuromuscular blocking drugs. The phenomenon was described first by Dundee and Gray for tubocurarine in 1953 [1], and has since been demonstrated for pancuronium [2] and, more recently, for vecuronium and atracurium [3]. However, the mechanism of such resistance is not clear. Furthermore, the route of elimination of laudanosine, one of the principal metabolites of atracurium, is not clearly defined. It has been shown that patients with renal failure develop greater plasma concentrations of laudanosine than do normal controls [4], but more recent work suggests that the renal clearance of laudanosine is a minor fraction of total clearance [5], as has been shown in the dog [6] and rat [7]. It is known that laudanosine undergoes significant hepatic excretion in the cat [8], although not in the dog [6]. The importance of the hepatic route of laudanosine excretion in man is not clear, although laudanosine excretion is altered in patients with biliary obstruction [9].

The present study was designed to define the pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis in comparison with a group of healthy patients undergoing general surgical procedures.

PATIENTS AND METHODS

Patients (table I)

We studied eight patients with hepatic cirrhosis scheduled to undergo elective sclerotherapy of oesophageal varices. Seven healthy patients undergoing minor surgery requiring the use of neuromuscular blockade (for example inguinal hernia repair, closure of colostomy) served as controls. All patients gave informed consent and the study was approved by the Hospital Ethics Committee.

In six of the patients with cirrhosis, the diagnosis had been confirmed by liver biopsy. In the other two, who had refused to undergo liver biopsy, the diagnosis of cirrhosis rested on the history, clinical examination and biochemical data. The aetiology of the cirrhosis was alcoholic in four patients, chronic active hepatitis in one patient, primary biliary cirrhosis in one patient and was unknown in two patients.

None of the control patients was receiving regular oral medication. Of the patients with cirrhosis, six received regular diuretics (four

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TABLE I. *Age and weight (mean (SD)) and sex of the patients studied*

	Control group ($n = 7$)	Cirrhotic group ($n = 8$)
Age (yr)	56.1 (10.7)	59.3 (14.6)
Weight (kg)	69.4 (14.7)	68.9 (8.9)
Sex (M:F)	5:2	5:3

spironolactone and two frusemide) and four were receiving H_2-receptor antagonists (three ranitidine and one cimetidine).

The preoperative laboratory data for the two groups are summarized in table II. Functional classification [10] of the patients with cirrhosis is given in table III.

Anaesthesia

Patients were premedicated with promethazine 50 mg on the evening before the operation, except

TABLE II. *Mean (SD) biochemical and haematological data (with normal range) for the control and cirrhotic groups. *Significant difference between the two groups, Mann–Whitney rank sum test:* $P < 0.05$

	Control group ($n = 7$)	Cirrhotic group ($n = 8$)	
Urea (mmol litre^{-1}) (3.0–7.0)	4.5 (0.7)	6.3 (3.9)	ns
Creatinine (µmol litre^{-1}) (60–110)	95 (17.2)	87 (12.0)	ns
Alkaline phosphatase (u. litre^{-1}) (35–130)	75 (24)	182 (116)	*
Total protein (g litre^{-1}) (57–76)	69.7 (3.3)	68.8 (5.2)	ns
Albumin (g litre^{-1}) (30–50)	42.5 (3.0)	36.2 (5.6)	*
Globulin (g litre^{-1}) (23–35)	27.2 (4.4)	32.5 (3.6)	*
Total bilirubin (µmol litre^{-1}) (2.0–17.0)	7 (2.3)	36 (24.9)	*
Alanine aminotransferase (u. litre^{-1}) (7–45)	26 (6.4)	37 (16.3)	*
Gamma-glutamyl transferase (u. litre^{-1}) (0–65)	49 (28.7)	119 (133)	ns
Haemoglobin (g dl^{-1})	13.9 (1.47)	11.1 (1.48)	*
Platelets (10^9 litre^{-1}) (150–400)	260 (23)	109 (40.2)	*
Prothrombin ratio (1.0)	—	1.56 (0.26)	

TABLE III. *Classification of the patients with cirrhosis in terms of hepatic functional reserve [10] and numbers in each group*

	Child's group [10]		
	A	B	C
Serum bilirubin (µmol litre^{-1})	< 34	34–50	> 50
Serum albumin (g litre^{-1})	> 35	30–35	< 30
Ascites	None	Easily controlled	Poorly controlled
Neurological disorder	None	Minimal	Advanced
Nutrition	Excellent	Good	Poor
No. patients	4	3	1

one patient with cirrhosis who exhibited signs of encephalopathy (Child's group C), in whom it was omitted. Anaesthesia was induced with thiopentone 150–400 mg; opioids were omitted in the patients with cirrhosis, but the control group received fentanyl 75–200 μg at induction. Neuromuscular blockade was provided by atracurium 0.6 mg kg^{-1}. The trachea was intubated and anaesthesia was maintained by controlled ventilation with 66% nitrous oxide in oxygen, supplemented with enflurane up to 1%. End-tidal carbon dioxide concentration was monitored using a Datex "Normocap" and maintained in the range 4–5.5%. After the completion of surgery, residual neuromuscular blockade was antagonized with neostigmine 2.5 mg and atropine 1.2 mg. All i.v. drugs were given through a cannula in a vein in the dorsum of one hand; the cannula was flushed with 0.9% saline 5 ml before and immediately after the administration of atracurium. Venous blood samples were taken from a 14-gauge cannula placed in an antecubital vein of the opposite arm.

Analytical technique

Blood samples (2.5 ml) were taken into heparinized syringes before injection of atracurium and at 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240, 300 and 360 min after the administration of atracurium. The sample was transferred immediately to a tube containing 0.02 ml of sulphuric acid 1.5 mol $litre^{-1}$ and cooled in ice for 30 s during transfer to an adjacent laboratory. Plasma was separated without delay using an MSE Centaur 2 centrifuge and four 0.2-ml aliquots were transferred into 1.5-ml polypropylene tubes containing 0.8 ml of sulphuric acid 0.015 mol $litre^{-1}$. These samples were frozen immediately in liquid nitrogen and stored at −20 °C until required for analysis.

Fresh standards were prepared for each patient. Using 0.2-ml aliquots of the patient's plasma taken before injection of atracurium, and a series of five drug dilutions, a standard curve was constructed for a range of plasma concentrations up to 10 μg ml^{-1} for atracurium and 500 ng ml^{-1} for laudanosine.

Extraction of atracurium and laudanosine from plasma (by the method of Simmonds [11]) was undertaken separately, in duplicate, for each drug. Before extraction, an internal standard of N-methyl laudanosine 20 μl (2.5 μg ml^{-1}) was added to each sample for assay of laudanosine; an internal standard of tubocurarine 20 μl (150 μg ml^{-1}) was added to each sample for the assay of atracurium.

Extracted samples were assayed by high performance liquid chromatography (HPLC). Each drug was assayed separately using an isocratic elution. For atracurium, a Spherisorb CN 5-μm column and a mobile phase of acetonitrile: sodium sulphate 0.02 mol $litre^{-1}$ in sulphuric acid 0.005 mol $litre^{-1}$ (60:40) was used. For the laudanosine assay a Partisil 10-μm strong cation exchange column and a mobile phase of acetonitrile: sodium sulphate 0.012 mol $litre^{-1}$ in sulphuric acid 0.005 mol $litre^{-1}$ (70:30) was used. For both drugs the column temperature was 50 °C and the mobile phase flow rate was 2 ml min^{-1}.

A 3000 Perkin–Elmer fluorescence detector was used for drug detection with excitation set at 280 nm and emission at 320 nm. Peak heights were measured directly from a chart recorder and peak height ratios of drug to internal standard were used to calculate drug concentration.

Analyses were completed within 4 days of sample collection. Because of technical problems, some samples were lost during analysis. Results for atracurium were available therefore for all but one of the patients with cirrhosis and for laudanosine in all but one of the controls. In two of the eight patients with cirrhosis, plasma laudanosine concentration was measured only up to 240 min after atracurium injection.

Data for plasma concentrations of atracurium were fitted to a two-component exponential by weighted non-linear least squares analysis and kinetic parameters calculated using the convention of Ward and colleagues [12].

Plasma concentrations of laudanosine between 180 and 360 min after atracurium injection were fitted to a single exponential term from which the elimination half-life was calculated. Total area under the plasma concentration–time curve was calculated as the sum of the area up to 360 min, evaluated by the trapezoidal rule, plus the area under the extrapolated plasma concentration curve from 360 min to infinity [13]. The total area under the curve was used to calculate the plasma clearance of laudanosine and, together with the terminal half-life, the volume of distribution was calculated. As laudanosine was not injected as a single bolus, but formed *in vivo* from atracurium, it was not possible to calculate model compartmental volumes or distribution rate constants.

The Mann–Whitney rank sum test was used for

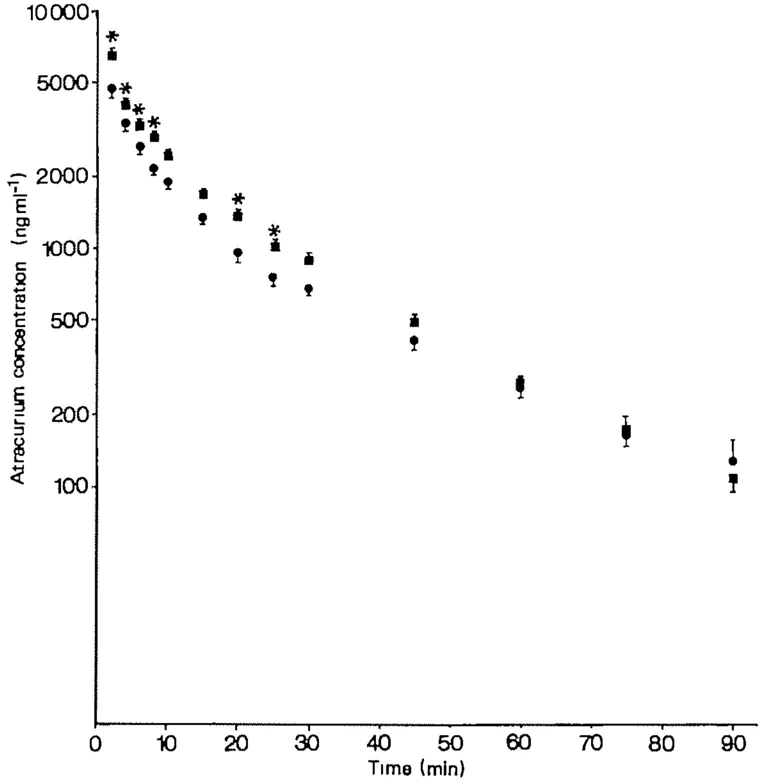

FIG. 1. Mean (SEM) plasma atracurium concentration (ng ml^{-1}) with time (min). ■ = Healthy group; ● = cirrhotic group. *Significant difference between the two groups using the Mann–Whitney rank sum test: $P < 0.05$.

statistical comparisons between the different groups of data [14].

RESULTS

Standard curves were linear over the measured range of drug concentration. The laudanosine assay was sensitive to 5 ng ml^{-1} and the coefficient of variation was typically 9 % at 100 ng ml^{-1}. The atracurium assay was sensitive to 25 ng ml^{-1} and had a coefficient of variation of 8 %.

Atracurium

Comparisons at each sample time revealed that the atracurium concentration was significantly lower in the patients with cirrhosis at 2, 4, 6, 8, 20 and 25 min after injection, although the difference failed to reach significance at the 10- and 15-min sample times (fig. 1).

The derived pharmacokinetic indices are shown in table IV. No significant difference was found in the distribution ($T_{\frac{1}{2}}^{\alpha}$) or elimination ($T_{\frac{1}{2}}^{\beta}$) half-lives of atracurium in the patients with cirrhosis compared with the healthy controls. Both the central (V_1) and the total (V^{β}) volumes of distribution, and the clearance (Cl) were significantly greater in the cirrhosis group.

Laudanosine

Analysis at each time shows that the plasma concentration of laudanosine in the cirrhosis group was significantly lower than the controls at 2, 4, 6, 8 and 10 min, and significantly greater at 360 min after the injection of atracurium. At other times there was no significant difference between the two groups (fig. 2).

Derived parameters are compared in table V for the control group and for the six patients with cirrhosis in whom sampling extended to 360 min. Both the elimination half-life and the total volume of distribution were significantly greater in the cirrhotic patients than in the controls. There was no significant difference in the clearance of laudanosine between the two groups.

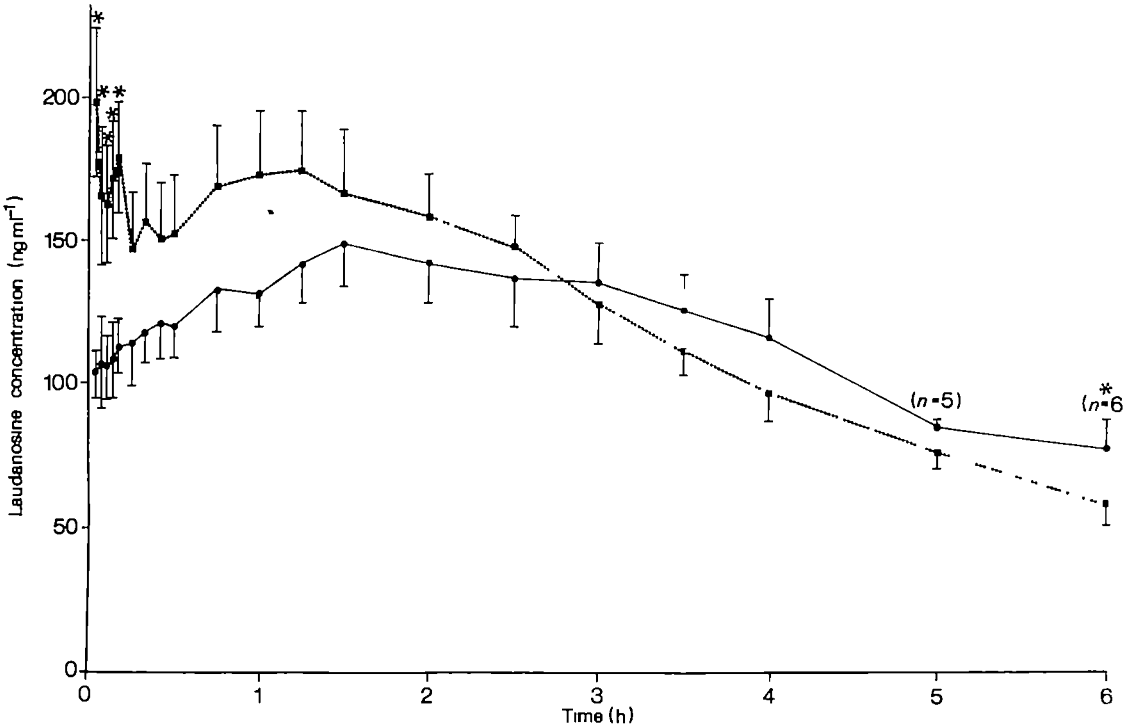

FIG. 2. Mean (SEM) plasma laudanosine concentration (ng ml^{-1}) with time (h). ■ = Healthy group; ● = cirrhotic group. *Significant difference between the two groups using the Mann–Whitney rank sum test: $P < 0.05$.

TABLE IV. *Derived pharmacokinetic parameters for atracurium (mean (SD)). *Significant difference between the two groups using the Mann–Whitney rank sum test:* P < *0.05*

	Control group ($n = 7$)	Cirrhotic group ($n = 7$)	
$T_{\frac{1}{2}}^{\alpha}$ (μιν)	3.00 (1.01)	3.75 (1.56)	ns
$T_{\frac{1}{2}}^{\beta}$ (μιν)	20.9 (5.3)	24.5 (4.9)	ns
V_1 (*ml kg*$^{-1}$)	69.6 (22.6)	104.6 (39.7)	*
V^{β} (ml kg^{-1})	202.1 (71.4)	281.8 (71.2)	*
Cl (ml min^{-1} kg^{-1})	6.6 (1.2)	8.0 (1.7)	*

TABLE V. *Pharmacokinetic parameters for laudanosine (mean (SD)). *Significant difference between the two groups using the Mann–Whitney rank sum test:* P < *0.05*

	Control group ($n = 6$)	Cirrhotic group ($n = 6$)	
$T_{\frac{1}{2}}$ (min)	168 (51.3)	277 (71.8)	*
V (litre kg^{-1})	1.97 (0.58)	2.63 (0.75)	*
Cl (ml min^{-1} kg^{-1})	8.3 (2.1)	6.9 (1.7)	ns

DISCUSSION

The pharmacokinetics of atracurium and its derivative, laudanosine have been studied previously in healthy patients and patients in renal failure [4,5,15,16] and in patients suffering from acute hepatic failure [17]. The present study has compared the pharmacokinetics of atracurium and laudanosine in adult patients chronically ill from hepatic cirrhosis with a group of healthy patients well matched for age, weight and sex.

The patients with cirrhosis in the present study, who were undergoing an elective course of treatment, had much less derangement of hepatic function than those suffering from acute hepatic failure reported by Ward and Neill [17]. Indeed, most of the present patients were classified to Child's groups A and B (table III). However, the degree of liver dysfunction was similar to that of a group of patients in whom resistance to atracurium was demonstrated [3].

It is accepted that elimination of atracurium from the body is dependent chiefly upon Hofmann elimination and ester hydrolysis, rather than organ-based metabolism and excretion [16]. The present finding that the elimination half-life of atracurium is similar in patients with hepatic cirrhosis and patients with normal hepatic function lends support to this concept. The tendency to a small and statistically insignificant prolongation of elimination half-life in the patients with cirrhosis (table IV), is similar to that reported in a group of patients with acute hepatic failure [17], and in patients with chronic renal failure [5,15].

Both the central and total volumes of distribution of atracurium were increased in the cirrhosis group. The volumes of distribution of several other non-depolarizing neuromuscular blocking drugs, for example pancuronium and fazadinium, are also increased in patients with cirrhosis [18,19]. An increased volume of distribution may provide a kinetic correlate for the earlier pharmacodynamic findings of Bell and colleagues [3] that, in patients with cirrhosis, the time to maximum depression of the twitch response following a bolus dose of atracurium was prolonged from 109 to 186 s, whilst time to 20% recovery of A′/A of the train-of-four was shortened from 43 to 34 min. The volumes of distribution of atracurium in the healthy patients reported here are similar to those found by Fahey and co-workers (V_1 60 ml kg^{-1}; V_{area} 182 ml kg^{-1}) [15], although they are rather larger than those reported by Ward and colleagues [12].

The clearance of atracurium was greater in patients with cirrhosis. Presumably, this reflects the spontaneous degradation of atracurium throughout its increased total volume of distribution, rather than any difference in its treatment by specific organs.

Taking into account the different doses of atracurium used in different studies, the magnitude and time course of the plasma concentration of laudanosine in the healthy patients reported here are in good agreement with previous results [4,5]. The peak laudanosine concentration, 198 ng ml^{-1}, was reached 2 min after the injection of atracurium. The time course of the plasma laudanosine concentration in the patients with cirrhosis was different, however, achievement of the peak laudanosine concentration (149 ng ml^{-1}) being delayed until 90 min after the administration of atracurium.

In descriptive terms, the present results demonstrate that, during the first 10 min after a bolus of atracurium, the plasma concentration of laudanosine was lower in patients with cirrhosis, whereas after 6 h the plasma concentration was significantly higher in that group.

Detailed consideration of the pharmacokinetics of laudanosine in man following a bolus of atracurium is complicated, as the extent, rate and time course of generation of laudanosine are not easily defined. Although there is evidence from *in vitro* work [20] that each molecule of atracurium is degraded to two molecules of laudanosine, there are many available pathways and it is conceivable that some of the intermediary metabolites are metabolized or excreted by routes which do not lead to the appearance of laudanosine in plasma. Although attempts have been made to overcome the limitations of a descriptive approach by fitting data on plasma concentration of laudanosine to a simple model [5], the model-independent ap- [5]. The clearance of laudanosine in the patients certain parameters. Thus it has been found that the terminal half-life of laudanosine, estimated from plasma concentration between 3 and 6 h after atracurium injection, was prolonged significantly, by a factor of about 1.6, in patients with cirrhosis. The clearance of laudanosine in the present group of healthy patients (8.3 ml kg^{-1} min^{-1}) is in reasonable agreement with the value of 10 ml kg^{-1} min^{-1} found by Ward and colleagues [5]. The clearance of laudanosine in the patients with cirrhosis was not significantly lower than in the healthy group, suggesting that the main cause for the prolonged elimination of laudanosine from the patients with cirrhosis lies with the expanded distribution volume.

It is tempting to relate the increased volumes of distribution of atracurium and laudanosine in the patients with cirrhosis to the salt and water retention which occur in this condition. In individual patients, however, the volume of distribution of atracurium was not related to the degree of ascites, which was severe in only one patient. Furthermore, the lipophilicity of laudanosine and its high volume of distribution render salt and water retention unlikely as the sole explanation for our findings. The extent of plasma protein and tissue binding of both atracurium and laudanosine is uncertain, and so it is difficult to speculate on the influence of these processes on the present results. At present, therefore, the cause of the alterations in the pharmacokinetics of atracurium and laudanosine in patients with cirrhosis remains uncertain.

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IS VECURONIUM A LONG-ACTING NEUROMUSCULAR BLOCKING AGENT IN NEONATES AND INFANTS?

O. A. MERETOJA

SUMMARY

Vecuronium was used as the only neuromuscular blocking agent in 81 paediatric patients (neonates to adolescents) during fentanyl and nitrous oxide anaesthesia. The thenar electromyogram was used to monitor neuromuscular blockade. Neonates and infants had a mean requirement of vecuronium 105 µg kg^{-1} during the first 1 h of anaesthesia, to establish and maintain 90–98% neuromuscular blockade, compared with a mean requirement of 217 µg kg^{-1} for children aged 3–10 yr ($P < 0.05$). Vecuronium 100 and 150 µg kg^{-1} maintained neuromuscular blockade > 90% for 59 and 110 min, respectively, in neonates and infants, but only for 18 and 38 min in children and for 37 and 68 min in adolescents ($P < 0.05$). Vecuronium may be regarded as a long-acting neuromuscular blocking agent in patients aged less than 1 yr.

We have previously shown that the ED_{50} and ED_{95} of vecuronium are 40% smaller in neonates and infants than in children aged between 3 and 10 yr [1]. The spontaneous recovery rate is also strongly dependent on age: the recovery index is 18–20 min in infants and 9–10 min in children [2–3]. The maintenance requirements for vecuronium have not been determined in paediatric patients. The aim of this study was to investigate the effect of age on the maintenance requirements and the duration of action of vecuronium during prolonged anaesthesia in infants and children.

PATIENTS AND METHODS

We studied 81 patients of ASA grades I and II scheduled to undergo an elective surgical procedure lasting a minimum of 90 min. The patients were healthy and were not receiving medications known to affect neuromuscular transmission or renal or hepatic function. The study was approved by the Ethics Committee of the Children's Hospital, University of Helsinki, and consent was given by the parents.

The patients were classified into nine groups of nine, delimited by the ages 3 months, 1, 2, 3, 5, 7, 10 and 13 yr. The youngest age group included seven neonates (12–27 days old and weighing 3.3–4.2 kg) whose gestational ages had been 38–41 weeks. The average age of the second group was 6.2 months (range 3.9–8.0 months).

Dextrose 5% with sodium chloride 60 mmol litre^{-1} was administered at a rate of 2–4 ml kg^{-1} h^{-1} throughout anaesthesia. Premedication consisted of either methohexitone 15 mg kg^{-1} per rectum (3 months to 4 yr) or flunitrazepam 0.08 mg kg^{-1} by mouth (maximum dose 2.0 mg) (1-16 yr). Anaesthesia was induced with fentanyl 3 µg kg^{-1} and thiopentone 2–4 mg kg^{-1}. Ventilation was controlled with 67% nitrous oxide in oxygen to maintain the end-tidal carbon dioxide concentration at 5.0–5.5%. Body temperature was maintained between 36 and 37 °C. No volatile anaesthetic agent was used.

Neuromuscular transmission was monitored by electromyography (EMG) (Relaxograph, Datex, Finland). Surface electrodes were placed over the ulnar nerve near the wrist, over the adductor pollicis muscle on the thenar eminence, and over the proximal phalanx of the middle finger. The thenar EMG was recorded with train-of-four stimulation (TOF) (2 Hz at 20-s intervals). After calibration of the equipment, vecuronium was administered in divided doses to achieve 95% depression of the first twitch response (95%

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TABLE I. *ED_{95} and dose requirement of vecuronium, and duration of > 90 % neuromuscular blockade maintained by vecuronium in paediatric patients (means (SEM)). Significant differences: †from groups < 2, < 3, < 5, < 7, < 10, < 13 and < 17 yr (Anova and Tukey test); §from groups < 3, < 5, < 7, < 10 and < 13 yr; ¶from groups < 5, < 7 and < 10 yr*

Age group	ED_{95} (µg kg^{-1})	Requirement in 60 min (µg kg^{-1})	Duration 100 µg kg^{-1} (min)	Duration 150 µg kg^{-1} (min)
< 3 months	49 (6)§	106 (7)§	60 (7)†	111 (13)†
3 months–< 1 yr	47 (3)§	104 (3)§	57 (3)†	109 (5)†
1–< 2 yr	58 (6)	134 (9)¶	39 (4)¶	72 (6)¶
2–< 3 yr	69 (4)	185 (12)	24 (3)	49 (6)
3–< 5 yr	80 (4)	207 (10)	19 (2)	39 (3)
5–< 7 yr	75 (5)	223 (19)	18 (2)	37 (4)
7–< 10 yr	84 (5)	221 (19)	18 (3)	38 (6)
10–< 13 yr	74 (7)	185 (18)	25 (4)	48 (6)
13–< 17 yr	52 (3)¶	143 (7)¶	37 (3)¶	68 (6)¶

neuromuscular block) over 5–8 min, and the trachea was intubated. Incremental doses of vecuronium 10–15 µg kg^{-1} were given whenever the first twitch of the TOF recovered to 10 % of the control value. If increments were needed at regular intervals, vecuronium was administered by continuous infusion. Neuromuscular blockade was maintained between 90 and 98 % throughout the study period in every patient.

Three or four doses of vecuronium were given during establishment of the initial 95 % blockade. The individual ED_{95} doses for vecuronium were determined after log-probit analysis was used to determine the individual vecuronium dose–response curves. The individual vecuronium requirement during the first 1 h of anaesthesia was calculated and the duration of neuromuscular blockade > 90 % maintained by cumulative doses of vecuronium 100 and 150 µg kg^{-1} measured. Analysis of variance, with Welch modification in cases of unequal variances, was used for statistical analysis (BMDP Statistical Software 7D, Berkeley, California). The Tukey studentized range method was used to compare the mean ED_{95} doses, and the between-group requirements and durations of effect of vecuronium. $P < 0.05$ was considered statistically significant. Values are expressed as mean (SEM).

RESULTS

In patients younger than 1 yr the ED_{95} of vecuronium was 40 % less than in patients aged 3–10 yr ($P < 0.01$), but comparable to the ED_{95} for adolescents (table I). During the first 1 h of anaesthesia, vecuronium requirements of neonates and infants were identical, but were only 48 % and 73 % of the requirements for children aged 3–10 yr and adolescents, respectively (table I). The cumulative 100-µg kg^{-1} dose of vecuronium maintained neuromuscular blockade > 90 % in infants for 58 min, compared with only 18 min in children aged 3–10 yr ($P < 0.001$) and 37 min in adolescents ($P < 0.01$) (fig. 1). There were similar differences in the durations of blockade > 90 % maintained by the cumulative 150-µg kg^{-1} dose of vecuronium.

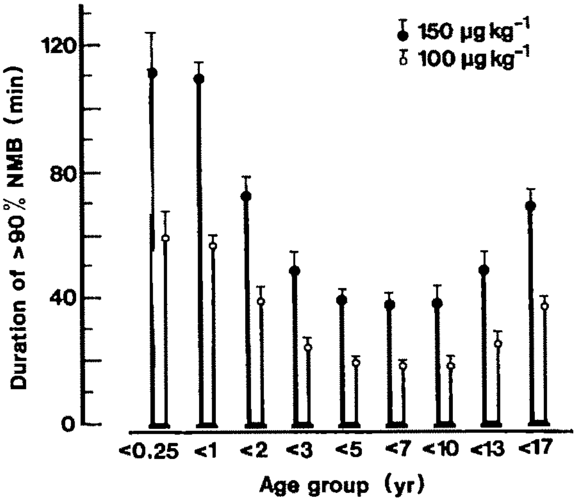

FIG. 1. Mean (SEM) duration of the > 90 % neuromuscular blockade maintained by cumulative doses of vecuronium 100 and 150 µg kg^{-1} in different age groups of paediatric patients. Note the marked prolongation of effect in infants compared with older children and adolescents.

DISCUSSION

The present study is the first to analyse of the maintenance dose requirements of vecuronium in different age groups of paediatric patients. Requirements for vecuronium in neonates and infants (aged up to 1 yr) were approximately 50 % of those in children aged 3–10 yr. Furthermore, cumulative 100- and 150-µg kg^{-1} doses of vecuronium could maintain surgical neuromuscular blockade in infancy for almost 1 and 2 h, respectively, while the duration was less than 20 and 40 min in children aged 3–10 yr. Vecuronium is clearly not an intermediate-acting neuromuscular blocking agent in infancy compared with childhood. In contrast, the steady-state infusion requirement for atracurium is similar in children of all ages greater than 1 month [4, 5].

We have shown previously that the ED_{95} of vecuronium is identical in neonates and older infants (47 µg kg^{-1}), but significantly less than in children aged 3–10 yr (81 µg kg^{-1}) [1]. The present results are comparable to these values. The lesser ED_{95} in infancy may result from the immaturity of neuromuscular transmission in these subjects. Marked differences have been found in the the pharmacodynamics of vecuronium between infants and children [2, 3]. The rate of spontaneous recovery of neuromuscular blockade was halved in infants compared with children. Clearance of vecuronium has been found to be comparable in infants and children, but the distribution volume was greater in infants [6]. This leads to a slower rate of recovery from neuromuscular blockade in infants compared with children. In contrast, the spontaneous recovery rate of atracurium is only slightly slower in neonates and infants than in children [7].

The ED_{95} values for pancuronium, tubocurarine and dimethyltubocurarine are identical in infants and children [8–10]. Furthermore, the rates of recovery from neuromuscular blockade induced by pancuronium and dimethyltubocurarine are similar in infants and children [8, 10], indicating that both are long-acting non-depolarizing neuromuscular blockers in both groups. Tubocurarine, however, may be a more long-acting agent in infants than in children [9, 11, 12]. In contrast, prolongation of effect and diminished dose requirement in neonates and infants appear to be features unique to vecuronium. The mean hourly maintenance requirement of a long-acting neuromuscular blocking agent, such as pancuronium, is 60 % of the ED_{95} [13]. In the present study, the 150-µg kg^{-1} dose of vecuronium maintained neuromuscular blockade > 90 % for 20 min longer than the 100-µg kg^{-1} dose in children aged 3–10 yr. The hourly maintenance requirement of these children was thus 210 % of the ED_{95}, which is appropriate for an intermediate-acting neuromuscular blocking agent. However, in neonates and infants the hourly requirement was 130 % of the ED_{95}. This difference, together with the marked prolongation of the spontaneous recovery rate in infancy, suggests that the neuromuscular blocking effects of vecuronium in neonates and infants tend to similarities with those of a long-acting neuromuscular blocking agent.

The ED_{95} of vecuronium in adolescents was less and the duration of blockade > 90 % longer following both 100 and 150 µg kg^{-1}, compared with the values in children aged 3–10 yr. These findings may be clinically important, but do not indicate that vecuronium is not an agent of intermediate duration of action in this age group. Vecuronium 150 µg kg^{-1} maintained neuromuscular blockade > 90 % for 31 min longer than did 100 µg kg^{-1} in adolescents. The calculated hourly maintenance requirement would then be 200 % of the ED_{95}, confirming an intermediate duration of effect. Although children aged 3–10 yr showed the shortest duration of blockade > 90 %, their vecuronium requirement was comparable to the requirements of other children and adolescents when related to individual ED_{95} values.

Prolonged duration of action of vecuronium is thus seen only in neonates and infants. A dose of 100 µg kg^{-1} corresponds with 1.9 mg m^{-2} in neonates and infants. The same dose per unit body surface area would correspond with 75 and 57 µg kg^{-1} in children aged 3–10 yr and adolescents, respectively. Therefore, if vecuronium is administered by calculating dose on the basis of body surface area instead of body weight, the differences in duration of effect between different age groups is accentuated.

The maintenance dose requirement for vecuronium is related to the age of the paediatric patient. A dose of 100 µg kg^{-1} produces neuromuscular blockade > 90 % of almost 1 h duration in infancy, but of only 18 min in children aged 3–10 yr. Vecuronium tends to have an effect in neonates and infants which is similar to that of a long-acting neuromuscular blocking agent.

ACKNOWLEDGEMENTS

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EFFECT OF SURFACE ELECTRODE POSITIONING ON THE COMPOUND ACTION POTENTIAL EVOKED BY ULNAR NERVE STIMULATION IN ANAESTHETIZED INFANTS AND CHILDREN

I. KALLI

SUMMARY

The effect of surface electrode positioning on the evoked compound action potential (ECAP) was studied during inhalation anaesthesia without neuromuscular blockade. The ECAP of five full-term infants (aged 2–20 weeks) and five children (age 1–10 yr) was recorded with a neuromuscular relaxation monitor (Relaxograph, Datex) after supramaximal ulnar nerve stimulation. The five recording electrode positions compared were: thenar (adductor pollicis) v. *second finger (TD2); thenar* v. *second dorsal metacarpal interspace (TM2); hypothenar* v. *fifth finger (HD5); hypothenar* v. *fourth dorsal metacarpal interspace (HM4); thenar* v. *hypothenar (TH). The ECAP was steady at positions TD2 and HD5, but marked variation and baseline drift was found at TM2, HM4 and TH. The ECAP peak-to-peak amplitudes were twice as great in children compared with infants. The hypothenar ECAP was liable to stimulus artefact interference because of the short onset latency at HD5 (2.2(SD 0.4)ms), whereas the adductor pollicis (3.0 (SD 0.5)ms) position (TD2) yielded reliable results.*

Neurophysiological monitoring of muscle relaxation is qualitatively and quantitatively more precise than visual or tactile evaluation of neuromuscular blockade [1]. Monitoring of blockade based on the evoked compound action potential (ECAP) has been used increasingly in clinical anaesthesia [2, 3].

The small size of an infant may make it technically difficult to position the monitoring electrodes [4]. Monitoring of blockade may be liable to interference when the surface electrodes have to be located near each other on a small arm. The immature neuromuscular junction [5], together with the relatively slow nerve conduction velocity of the newborn [6], may also influence the response.

The present study was designed to determine the effects of electrode position on the ECAP from ulnar nerve stimulation in anaesthetized infants and children.

PATIENTS AND METHODS

After the approval of the Ethics Committee of the Children's Hospital, five full-term infants (age 2–20 weeks) (A–E) and five children (age 1–10 yr) (F–K), with no disease and receiving no medication affecting the neuromuscular junction, were selected for the study (table I).

Patients up to 1 year of age received no premedication and anaesthesia was induced with isoflurane by face mask. In older children induction was with isoflurane ($n = 3$) or halothane ($n = 2$). Three were premedicated with oral benzodiazepines (patients H, J, K) (table I). Three patients (A, J, K) did not accept inhalation induction and sleep was induced with an appropriate dose of barbiturate.

Atropine 0.01 mg kg^{-1} was given i.v. before tracheal intubation, which was facilitated by suxamethonium 1 mg kg^{-1} i.v. in six patients (A, C, D, H, J, K). After induction of anaesthesia, a

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TABLE I. *Details of patients studied*

Patient	Age	Gestation (weeks)	Weight (kg)	Operation
A	14 day	40	3.8	Orthopaedic (extremity)
B	18 day	42	4.1	Orthopaedic (extremity)
C	22 day	37	4.3	Urology (nephrectomy)
D	36 day	42	4.5	Orthopaedic (extremity)
E	4.7 month	40	6.9	Orthopaedic (extremity)
F	1.0 yr		8.7	Neck tumour (excision)
G	1.3 yr		10.0	Urology (endoscopy)
H	2.2 yr		14.1	Urology (plastic)
J	5.1 yr		17.2	Urology (plastic)
K	10.1 yr		31.3	Urology (plastic)

30-min period was allowed for stabilization and elimination of suxamethonium. No other neuromuscular blocking drug was used during the study. ECAP was recorded within 30–60 min of induction of anaesthesia, during the constant administration of 1.8–3.2% isoflurane or 1.5–2.0% halothane in 66% nitrous oxide and oxygen.

Ventilation was controlled and adjusted to achieve normocapnia. End-tidal carbon dioxide, ECG, arterial pressure and body temperature were monitored in all patients.

The arm was supported in a splint and the skin cleaned with alcohol before the disposable surface electrodes (Datex 57267 pre-gelled, diameter 12.5 mm) were attached for stimulation and recording purposes. The ulnar nerve was stimulated with a train-of-four (TOF) supramaximal square wave impulses of 0.1 ms duration at 2 Hz, the minimum delay between two adjacent TOF being 20 s. The supramaximal ECAP was determined with the automatic calibration provided by the neuromuscular relaxation monitor (Relaxograph, Datex). The maximum current of the device is limited to 70 mA. During automatic calibration the current is gradually increased until supramaximal ECAP is reached. The delivered current is then increased by 10% and constitutes the supramaximal stimulus used in the recordings.

The amplified, unfiltered ECAP response of the first stimulus of the TOF was transferred from the analogue output of the monitor to a digital storage oscilloscope (Gould OS4100) and recorded. In all recordings the ground electrode was positioned between the stimulating and recording electrodes, or as near as possible in order to reduce the stimulus artefact.

In the first part of the study, stimulating electrodes were positioned on the ulnar nerve near the wrist and five pairs of recording electrodes were compared by changing the recording pair of electrodes after every fifth TOF. In the second part of the study, four different positions of stimulation electrodes were compared, and ECAP was recorded from the electrodes on the hypothenar muscle and on the fifth finger (fig. 1).

The baseline for measurements of ECAP was defined as that recorded immediately before the stimulus artefact (fig. 2). The onset latency (DL) (duration from the start of the stimulus artefact to the negative deflection of the ECAP from the baseline) was determined. The duration (DZ) to the point where the ECAP negative wave returned to the baseline was measured also from the start of the stimulus artefact. The peak-to-peak amplitude and the amplitude of the ECAP negative wave were measured.

Unpaired Student's *t* test was used for statistical evaluation between age groups. $P \leqslant 0.05$ was regarded as statistically significant.

RESULTS

In the first part of the study, good quality biphasic ECAP were recorded when the active electrode was located on the adductor pollicis (TD2) or hypothenar (HD5) muscle motor point, the indifferent electrode being on either the second or fifth finger. When the indifferent recording electrode location was changed dorsally, to the second (TM2) or fourth (HM4) metacarpal interspace, summation ECAP of overlapping responses from different muscles was recorded, with marked interindividual variation and baseline drift. A

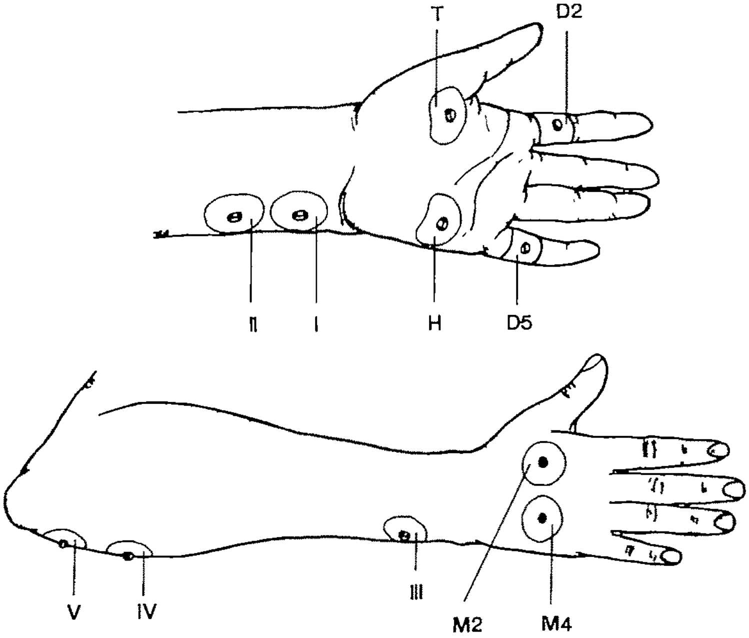

FIG. 1. Electrode positions. T and H denote the active recording electrodes on the thenar (adductor pollicis) and hypothenar muscle motor points. Indifferent recording electrodes were on the second and fifth finger (D2 and D5) and on the second and fourth dorsal metacarpal interspace (M2 and M4). Recording electrode pairs were TM2, TD2, HM4, HD5 and TH. Negative (I) and positive (II) stimulus electrodes were on the ulnar nerve near the wrist. Additional negative (IV) and positive (V) electrodes were on the ulnar groove, and a positive electrode on the dorsal side of the arm (III). Stimulus electrode pairs were I–II, I–III, I–V and IV–V.

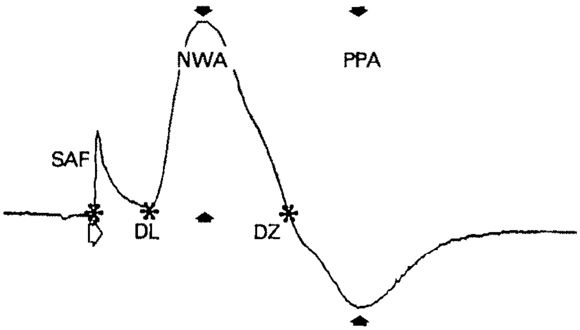

FIG. 2. Evoked compound action potential (ECAP) characteristics. Time intervals (asterisk) are measured from the outlined arrow. Black arrows indicate the amplitudes. SAF = stimulus artefact; NWA = negative wave amplitude; PPA = peak-to-peak amplitude; DL = onset latency; DZ = DL + negative wave duration.

similar variation was noted also in thenar–hypothenar (TH) recording, which was selected as an example of differential amplifier misuse, both recording electrodes being placed on an active muscle. Examples of waveforms of four patients are shown in figure 3.

The onset latency at position TD2 was significantly longer in infants younger than 1 yr (3.4 (SD 0.3) ms) than in older children (2.7 (0.3) ms) ($P = 0.008$), but not at the HD5 position (2.4 (0.3) and 2.0 (0.3) ms) ($P = 0.058$).

The peak-to-peak amplitudes of the older children at the TD2 position were twice as great (4.6 (0.6) mV) as those of the infants younger than 1 yr (2.0 (0.7) mV) ($P = 0.0002$). A similar finding was noted at the HD5 position (4.1 (0.8) and 2.1 (0.5)) ($P = 0.001$) (fig. 4). Onset latency and peak-to-peak amplitude for TD2 and HD5 positions are shown in table II. Supramaximal stimulus current ranged from 40 to 70 mA. No age-dependent difference in the duration of the ECAP negative wave (DZ – DL) was found. The recordings for children who had received suxamethonium did not differ from those of the other children.

In the second part of the study, no differences were noted when the positive stimulating elec-

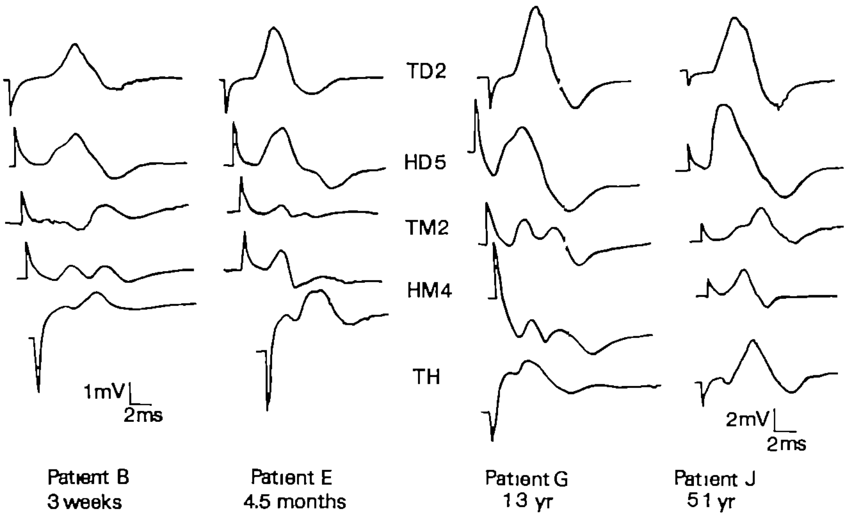

FIG. 3. Evoked compound action potential (ECAP) recordings of four study patients. The amplitude scale of the oldest child differs from the others. The amplitude and onset latency are age related. The short onset latency on the HD5 recordings compared with TD2 is demonstrated. Note the low amplitudes, individual variability and baseline drift in the three lowest recording positions (TM2, HM4, TH).

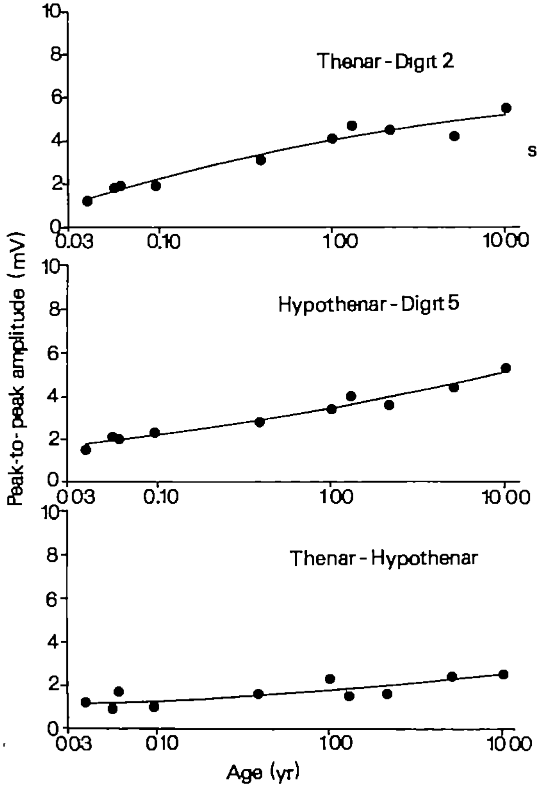

FIG. 4. Peak-to-peak amplitudes of three recording positions. Note the logarithmic age scale.

TABLE II. *Onset latency and peak-to-peak amplitude of thenar (TD2) and hypothenar (HD5) recordings. Differences between age groups were regarded to be statistically significant at* P < *0.05*

	Onset latency (ms)		Amplitude (mV)	
Patient	TD2	HD5	TD2	HD5
Group 1				
A	3.4	2.2	1.2	1.5
B	3.8	2.8	1.8	2.1
C	3.5	2.5	1.9	2.0
D	3.4	2.5	1.9	2.3
E	2.9	2.2	3.1	2.8
Mean (SD)	3.4 (0.3)	2.4 (0.3)	2.0 (0.7)	2.1 (0.5)
Group 2				
F	2.5	1.9	4.1	3.4
G	2.3	1.7	4.7	4.0
H	2.7	1.9	4.5	3.6
J	2.6	2.0	4.2	4.4
K	3.2	2.6	5.5	5.3
Mean (SD)	2.7 (0.3)	2.0 (0.3)	4.6 (0.6)	4.1 (0.8)
P	0.008	0.058	0.0002	0.001

trode was repositioned in any of three locations when the negative electrode was sited near the wrist. When the ulnar nerve was stimulated at the elbow, supramaximal stimulation could not be achieved in eight of the 10 patients with the highest current available from the monitor.

DISCUSSION

When neuromuscular relaxation is monitored in paediatric patients, the small size of the hand and arm may influence the recorded ECAP. It is affected also by the relatively slow nerve conduction of a newborn child [6] and the immaturity of the neuromuscular unit in the newborn compared with the adult [7]. The electrode diameter has been shown to affect the recording [8]. The same type of electrodes were used for all recordings in this study. The electrode size (12.5 mm diameter) was found to be relatively large for the smallest infants studied. Careful positioning was essential to avoid direct contact between the pre-gelled electrodes.

The median nerve may be stimulated unintentionally with supramaximal stimulation of the ulnar nerve, because an infant's wrist is small in proportion to the diameter of the stimulating electrodes covering the arm. The response in muscles innervated by the median nerve is likely to be submaximal. However, they may contaminate the desired ECAP if recording electrodes are not placed appropriately.

The differential pre-amplifier used in ECAP recordings amplifies the voltage difference between the electrodes. When positioning the active electrode on the motor point of a muscle, it is most important that the indifferent recording electrode is placed on an electrically neutral area. This study showed that, in a small child, the finger was a suitable site; good quality ECAP with a steady baseline was recorded in both the TD2 and the HD5 recordings.

In contrast, the dorsum of the hand was found to be a poor position for the indifferent recording electrode, and unpredictable, low amplitude ECAP with marked baseline drift was recorded at both TM2 and HM4. This finding may be attributed to simultaneous activation of the interosseus and lumbrical muscles. Submaximal median nerve stimulation, which is difficult to avoid in a small hand, may also have contributed.

As expected, the ECAP recorded between the electrodes on the thenar and hypothenar muscles (TH) was of poor quality. The action potentials in the thenar and hypothenar muscles are of different amplitudes and phases after ulnar nerve stimulation. Although a low voltage difference across the recording electrodes can be detected, the differential amplifier output remains low and unsteady.

Stimulus artefact is the current which flows rapidly along the skin to the recording electrodes after a stimulus, and thus has no relation to muscle activity. Positioning the ground electrode between the stimulating and recording pairs of electrodes is recommended in adults in order to reduce stimulus artefact [9]. This is seldom possible with standard ECG electrodes in infants, because of the small size of their hands. A more proximal position of the stimulating electrodes might theoretically reduce the stimulus artefact. In practice, however, it may be difficult to stimulate the ulnar nerve accurately near the elbow in children with a relatively thick subcutaneous tissue layer.

A sufficiently long onset latency, the time from stimulus to the main negative deflection of the ECAP, is necessary to separate the ECAP from the stimulus artefact. This is important in order to avoid errors in the monitoring of neuromuscular blockade. Onset latency is often affected most by the nerve conduction velocity and by the length of the stimulus conduction pathway. Because the stimulating and recording electrodes are near each other, the onset latency in small children would be short if it were not prolonged by the relatively slow nerve conduction velocity. In newborns the conduction velocity is only 50% that of the corresponding adult value [6].

The Relaxograph used has a 3-ms internal delay from the stimulus to avoid stimulus artefact, and integrates the ECAP signal from 3 to 13 ms after stimulation [10]. In the present study the onset latency in the adductor pollicis muscle aproximated to the internal delay (3.0 (0.5) ms for all patients). ECAP of the hypothenar muscles is more liable to stimulus artefact interference because the onset latency is even shorter (2.2 (0.4) ms). The difference is produced by the longer ulnar nerve conduction pathway to the thenar muscles.

Pugh, Kay and Healy showed a good correlation between the integrated area and amplitude of the ECAP in eight adults [11]. In the youngest of the patients in the present study, the absolute ECAP amplitudes were reduced, which is in agreement with Thomas and Lambert [6]. They showed that the hypothenar muscle negative deflection amplitude in newborns was one-third of the corresponding adult value. Because of the age-dependent variation in ECAP amplitude, a more accurate assessment of neuromuscular relaxation might be the integrated area of ECAP.

Accurate location of the negative electrode on the nerve was found to be important, whereas repositioning of the positive electrode caused no changes in the recorded response. This finding is in accord with the results of Berger, Gravenstein and Munson [12], who showed that the best stimulus response was obtained when the negative electrode was positioned upon a nerve.

ECAP recording using stimulation electrodes on the ulnar groove at the elbow was unsuccessful. In theory, stimulus artefact should be minimized with the long stimulus conduction pathway. In practice, supramaximal stimulation could not be achieved with the highest current of the monitor. Thus localization of the nerve near the ulnar groove by palpation was not sufficiently accurate for positioning the electrodes in small children.

In conclusion, optimum conditions for measurement of ECAP are achieved when the indifferent recording electrode is placed on an electrically neutral area, such as a finger, and the active recording electrode on the adductor pollicis muscle.

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HAEMODYNAMIC EFFECTS OF VECURONIUM

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SUMMARY

Three hundred and twenty adults (ASA grade I, both sexes,) received diazepam 10 mg by mouth (50% received atropine 7 μg kg⁻¹ in addition) i.m. 45 min before operation. Patients were then allocated randomly to undergo general anaesthesia with either a nitrous oxide–neurolept technique or nitrous oxide–halothane. Vecuronium was administered to 50% of the patients in each anaesthetic group and heart rate and arterial pressure were monitored. Vecuronium did not influence heart rate, or systolic or diastolic arterial pressures.

Many neuromuscular blocking agents exert cardiovascular side-effects, but these are thought to be infrequent following vecuronium bromide [1,2]. However, some authors have observed cardiovascular instability following administration of vecuronium [3–5]. These reports prompted us to examine if vecuronium exerts cardiovascular side effects and, in particular, possesses an inherent propensity to cause bradycardia.

PATIENTS AND METHODS

Three hundred and twenty adults (ASA grade I) (128 female), undergoing routine surgery, were admitted to this open study and allocated to receive either a nitrous oxide–neuroleptanaesthetic technique (NLA) or nitrous oxide–halothane anaesthesia. All patients received diazepam 10 mg by mouth as premedication and, following random allocation, 50 % of the patients in each anaesthetic group received atropine 7 μg kg^{-1} in addition; 50 % of each of these two groups of patients received vecuronium (table I). In this way eight groups were formed on a random basis. Details of the anaesthetic regimens are presented in table I.

Heart rate (HR), systolic (SAP) and diastolic (DAP) arterial pressures were measured before induction, and immediately before (0 min) and at intervals following the administration of vecuronium or saline (fig. 1) using an automatic non-invasive monitor (Dinamap). To reproduce clinical circumstances as closely as possible, vecuronium was given immediately following the post-induction measurements. The trachea was not intubated until the study was completed, in order to avoid effects of intubation on the cardiovascular system. Ventilation of the lungs was maintained by face mask. Data obtained before the administration of vecuronium or saline were analysed using the paired and unpaired Student's *t* tests; thereafter, three-way analysis of variance was used for all data.

RESULTS

The mean age of the patients was 34.7 yr and the mean weight 68.7 kg. There was no significant difference in the sex, weight or age distributions either between the vecuronium and non-vecuronium groups or between the atropine and non-atropine groups. However, the neuroleptanaesthesia group contained significantly more women than the halothane group (46.3 % *v.* 33.8 %, $P < 0.05$). The patients who received neuroleptanaesthesia were also slightly older (mean age 37 yr, compared with 32.3 yr in the halothane group) ($P < 0.005$).

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TABLE I. *Scheme of random allocation to groups, and details of anaesthetic regimens*

	Neuroleptanaesth. (n = 160)				Halothane (n = 160)			
Group:	1	2	3	4	5	6	7	8
n	40	40	40	40	40	40	40	40
Atropine	+	+	–	–	+	+	–	–
Vecuronium	+	–	+	–	+	–	+	–
Induction	Droperidol 0.15–0.3 μg kg^{-1} Fentanyl 3–5 μg kg^{-1} Thiopentone 1.5–3 mg kg^{-1}				Thiopentone 4–6 mg kg^{-1}			
Maintenance	Oxygen:nitrous oxide 1:2				Oxygen:nitrous oxide 1:2 1–1.5% Halothane			
	Saline (n = 80) or Vecuronium 100 μg kg^{-1} (n = 80)				Saline (n = 80) or Vecuronium 100 μg kg^{-1} (n = 80)			

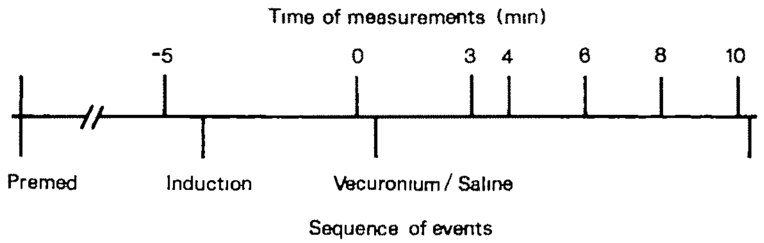

FIG. 1. Sequence of events and timing of cardiovascular measurements.

TABLE II. *Heart rate (beat min^{-1}) (mean (SD))*

		Time after vecuronium or saline (min)					
Group	Before induction	0	3	4	6	8	10
1	77 (18.6)	88 (18.0)	76 (10.6)	71 (08.4)	69 (14.6)	68 (13.5)	66 (12.6)
2	85 (19.0)	93 (17.8)	82 (16.2)	77 (14.4)	75 (14.8)	73 (11.8)	72 (13.8)
3	86 (19.0)	88 (18.2)	77 (20.1)	72 (15.9)	67 (14.3)	67 (16.1)	68 (12.0)
4	86 (14.7)	91 (15.7)	79 (15.5)	76 (11.0)	71 (15.0)	69 (14.2)	70 (14.7)
5	70 (16.0)	85 (15.0)	78 (12.7)	76 (13.0)	74 (13.4)	73 (13.3)	71 (15.0)
6	73 (15.6)	88 (14.4)	80 (12.8)	77 (13.0)	75 (11.1)	72 (13.7)	70 (13.9)
7	76 (17.4)	83 (15.0)	76 (14.9)	75 (11.0)	72 (10.8)	69 (10.0)	69 (10.3)
8	80 (17.0)	83 (17.0)	76 (12.8)	74 (12.5)	72 (12.9)	71 (13.6)	69 (12.7)

Cardiovascular data are presented in tables II, III and IV. Table V shows the pre-induction cardiovascular indices for patients who received atropine, compared with those who did not. There were no significant differences between the two groups in systolic and diastolic arterial pressures, but heart rate was significantly lower in the atropine-treated group ($P < 0.001$).

In all patients, heart rate increased significantly above the pre-induction value immediately following induction of general anaesthesia (table VI). This increase occurred regardless of whether or not atropine had been administered or the type of anaesthesia, and at this time there was no significant difference between the atropine and the non-atropine groups. Systolic and diastolic arterial pressures decreased significantly following induction of anaesthesia in all groups (table VI).

All groups demonstrated similar and significant ($P < 0.005$) decreases in heart rate following administration of vecuronium or saline (table VII).

Three-way analysis of variance of values ob-

TABLE III. *Systolic arterial pressure (mm Hg) (mean (SD))*

Group	Before induction	Time after vecuronium or saline (min) 0	3	4	6	8	10
1	124 (6)	110 (20)	96 (18)	94 (18)	94 (18)	93 (19)	94 (18)
2	127 (18)	115 (18)	100 (18)	97 (17)	99 (18)	100 (18)	101 (19)
3	128 (16)	119 (19)	102 (21)	97 (20)	94 (18)	95 (21)	95 (20)
4	128 (15)	113 (17)	101 (16)	97 (17)	95 (17)	94 (19)	98 (20)
5	130 (19)	118 (12)	113 (15)	111 (12)	108 (14)	109 (14)	108 (14)
6	127 (17)	118 (15)	113 (19)	111 (15)	107 (18)	106 (13)	107 (14)
7	131 (17)	116 (19)	110 (14)	108 (15)	107 (14)	107 (14)	105 (13)
8	126 (17)	113 (12)	109 (14)	108 (13)	107 (10)	106 (12)	105 (13)

TABLE IV. *Diastolic arterial pressure (mm Hg) (mean (SD))*

Group	Before induction	Time after vecuronium or saline (min) 0	3	4	6	8	10
1	77 (11)	69 (13)	65 (15)	63 (15)	63 (14)	62 (13)	63 (12)
2	78 (12)	71 (12)	64 (11)	62 (12)	61 (13)	63 (11)	65 (11)
3	82 (12)	76 (10)	67 (17)	64 (13)	61 (13)	62 (13)	62 (13)
4	82 (05)	69 (08)	64 (10)	61 (11)	61 (12)	61 (12)	64 (12)
5	85 (10)	80 (11)	74 (12)	74 (13)	73 (14)	72 (13)	71 (13)
6	80 (08)	76 (11)	72 (12)	74 (11)	70 (11)	68 (11)	68 (12)
7	81 (12)	74 (12)	69 (14)	68 (12)	66 (13)	66 (11)	65 (12)
8	78 (10)	72 (09)	68 (09)	67 (07)	67 (07)	67 (07)	65 (10)

TABLE V. *Comparison of the mean pre-induction cardiovascular values of atropine and the non-atropine treated patients (unpaired* t *test)*

	Atropine (n = 160)	No atropine (n = 160)	t	P
Heart rate (beat min^{-1})	76.25	82.00	2.98	< 0.001
Systolic AP (mm Hg)	127.00	128.30	0.69	ns
Diastolic AP (mm Hg)	80.00	80.00	0.65	ns

TABLE VI. *Change in cardiovascular values (after induction minus before induction) in patients treated with* (n = *160) and without atropine* (n = *160) (paired* t *test)*

	Atropine	Change	t	P
Heart rate (beat min^{-1})	Yes	+12.25	5.53	< 0.001
	No	+ 4.25	2.35	< 0.05
Systolic AP (mm Hg)	Yes	−11.75	5.41	< 0.001
	No	−13.00	5.87	< 0.001
Diastolic AP (mm Hg)	Yes	− 6.00	4.37	< 0.001
	No	− 7.50	4.64	< 0.001

TABLE VII. *Range of* t *values (paired* t *test) and significance of changes in heart rate from 0 to 3 min and 0 to 4 min for the eight groups*

Interval (min)	t (range)	P
0–3	3.47–4.25	< 0.005
0–4	4.43–4.93	< 0.005

tained at 0, 3, 4, 6, 8 and 10 min after administration of vecuronium (table VIII) revealed that the magnitude of the decrease in heart rate and systolic and diastolic arterial pressures was of the same order as that occurring in patients not receiving vecuronium. However, the reduction in heart rate was significantly greater in the group receiving neuroleptanaesthesia compared with the

TABLE VIII. *Three-way analysis of variance at 0 min (control) and 3, 4, 6, 8 and 10 min after administration of vecuronium. NLA = neuroleptanaesthesia; Hal = halothane; Vec = vecuronium; Non-vec = no vecuronium; Atr = atropine; Non-atr = no atropine*

Variable	Time (min)	Factor	*F*	*P*
Heart rate	0	NLA > Hal	= 8.97	< 0.005
Heart rate	0–10	Vec = Non-vec	< 4.00	ns
Systolic AP	0–10	Vec = Non-vec	< 4.00	ns
Systolic AP	3–10	NLA < Hal	> 17.8	< 0.001
Diastolic AP	0–10	Vec = Non-vec	< 4.00	ns
Diastolic AP	0–10	NLA < Hal	5.6–33.6	< 0.05–0.001
Diastolic AP	4–10	Atr > Non-atr	3.8–5.6	< 0.05

halothane group ($P < 0.005$). The hypotension in patients receiving halothane was significantly less than that in the neurolept group ($P < 0.001$). The decrease in diastolic arterial pressure in patients receiving atropine was greater than in the patients without this premedication ($P < 0.05$).

DISCUSSION

There was no significant difference in the reduction in heart rate and systolic arterial pressure which occurred following administration of vecuronium or saline (analysis of variance). Systolic and diastolic arterial pressures decreased more in the group receiving neuroleptanaesthesia compared with the halothane group. This was caused possibly by a more abrupt reduction in after-load or myocardial depression arising from the i.v. bolus administration of neuroleptic drugs compared with the slower build-up of halothane in the low inspiratory concentrations (1.0–1.5%) used in this study. However, the age and sex difference between the two groups could have contributed to the differences observed.

Krieg [6], Engbaek [7] and Mirakhur [8] and their respective colleagues demonstrated a similar lack of cardiovascular effects associated with the administration of vecuronium. However, Mirakhur and colleagues [8] observed bradycardia following administration of fentanyl and vecuronium; this responded promptly to i.v. atropine. However, both our study and that of Engbaek and colleagues [7] were carried out under conditions which avoided autonomic stimulation caused by surgery or tracheal intubation, and no effects were noted. Because of the rapid disappearance of vecuronium from plasma, any peripheral effects upon the cardiovascular system would be evident within 10 min of administration and there is no evidence that vecuronium crosses the blood–brain barrier in active amounts.

In this study, patients who received atropine with the premedication demonstrated a reduction in heart rate before induction of anaesthesia. This observation has been noted previously. Soon after i.m. administration of atropine in 0.2–0.3 mg doses, slowing of heart rate was observed by Morton and Thomas [9]; this finding was confirmed by Gravenstein and colleagues [10] and List and Gravenstein [11]. Kottmeier and Gravenstein [12] demonstrated that this bradycardia could be elicited in vagotomized dogs, whereas the biphasic effect of atropine on the P–R interval could be demonstrated only through vagal stimulation, low doses prolonging and higher doses shortening the interval. Loennerholm and Widerlov [13] compared atropine and methylatropine and suggested that a peripheral action of atropine was responsible for the related bradycardia. Thus low doses of atropine may result in bradycardia by two mechanisms: a direct agonistic effect on the heart and an indirect agonistic effect by modifying the vagal response. These findings are in accord with studies in humans by Thomas [14], Das and colleagues [15] and Mirakhur [16].

Immediately following induction of anaesthesia (0 min) there was no difference in heart rate between the patients who had received atropine and those who had not. Thus it would appear that general anaesthesia counteracts the effect of low-dose atropine in producing bradycardia. This finding is in accord with the work of Eger [17], who has shown that, when small doses of atropine are administered to anaesthetized patients, tachycardia rather than bradycardia results.

In conclusion, we have demonstrated that vecuronium did not influence heart rate or systolic arterial pressure during either nitrous oxide–neuroleptanaesthesia or nitrous oxide–halothane anaesthesia.

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CHANGES IN OXYGEN SATURATION DURING INHALATION INDUCTION OF ANAESTHESIA IN CHILDREN

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SUMMARY

Changes in oxygen saturation (Sa_{O_2}) *were studied during induction of anaesthesia in 48 healthy children receiving halothane or isoflurane for outpatient dental extractions. Substantial reductions in* Sa_{O_2} *occurred in more than 50% of the children given isoflurane and were associated with the irritant effects of this agent on the airway.* Sa_{O_2} *was largely unaltered during the use of halothane. These findings indicate that the airway complications caused by isoflurane may be associated with decreases in* Sa_{O_2}.

There have been conflicting reports on the suitability of isoflurane in paediatric outpatient dental anaesthesia. McAteer and others [1] believe that it is a satisfactory alternative to halothane, while Cattermole and colleagues [2] have taken the view that it cannot be recommended because of its pungency.

The clinical significance of the airway irritation caused by isoflurane has not been evaluated fully. The aim of this study was to compare the influence of airway irritation upon oxygen saturation (Sa_{O_2}) during halothane and isoflurane anaesthesia in children having outpatient dental extractions.

PATIENTS AND METHODS

Approval of the Research Ethics Committee and parental consent were obtained for the study. Forty-eight unpremedicated children, ASA grades I and II were allocated randomly to receive either halothane or isoflurane. The two groups did not differ with respect to age and weight (table I).

The management of the children was allocated equally between two consultant anaesthetists and all recordings were made by an independent observer. Heart rate and rhythm were monitored with an electrocardiogram and indirect arterial pressure with a Dinamap Vital Signs Monitor. Sa_{O_2} was measured continuously with the Durasensor probe of a Nellcor N100 pulse oximeter attached to the thumb of the left hand. Following measurements of heart rate, arterial pressure and Sa_{O_2}, and with the patient in the supine position, anaesthesia was induced with 33% oxygen in nitrous oxide administered through a Bain system via a face mask. Fresh gas flow was determined from the formula of Rose, Bryick and Froese [3]. The vapour concentration was increased by 0.5% increments every six breaths until a maximum of 3% halothane or 4% isoflurane was attained. If airway complications occurred, the vapour concentration was decreased by 0.5% When a normal respiratory pattern returned, the concentration was again increased incrementally. When a suitable depth of anaesthesia was achieved, the face mask was replaced with a McKesson nasal mask. Induction time was measured as the period from the placement of the face mask until the jaw was relaxed sufficiently to enable the dental surgeon to insert a mouth pack. Anaesthesia was

TABLE I. *Physical characteristics of children (mean (SD))*

	Isoflurane ($n = 24$)	Halothane ($n = 24$)
Age (yr)	6.07 (2.07)	6.18 ([illegible]31)
Weight (kg)	20.92 (5.24)	21.89 ([illegible]92)

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TABLE II. *Incidence of airway complications.* *$P < 0.05$; **$P < 0.001$

	Isoflurane ($n = 24$)		Halothane ($n = 24$)
Coughing	15	**	2
Breath-holding	13	**	0
Stridor	9	*	1
Salivation	8	*	1
Laryngospasm	4		0
Cyanosis	4		0

TABLE III. *Minimum* Sa_{O_2} *during induction*

Sa_{O_2} (%)	Isoflurane ($n = 24$)	Halothane ($n = 24$)
95–100	10	24
90–94	6	0
85–89	1	0
80–84	2	0
< 80	5	0

TABLE IV. *Minimum* Sa_{O_2} *During airway complications associated with isoflurane*

Complication	Frequency of complication (n)	Sa_{O_2} < 95%	Sa_{O_2} 95–100%
Coughing	15	2	13
Breath-holding	13	7	6
Salivation	8	4	4
Stridor	9	1	8
Laryngospasm	4	4	0
Cyanosis	4	4	0

TABLE V. *Duration of induction (mean (SD)).* *$P < 0.001$

	Isoflurane ($n = 24$)		Halothane ($n = 24$)
Time (min)	4.6 (1.2)	*	2.7 (0.9)

discontinued on completion of surgery and the patient was placed in the lateral position.

Arterial pressure and heart rate were recorded at 1-min intervals during the study. Complications such as salivation, breath-holding, coughing, stridor, laryngospasm and cyanosis were noted during induction of anaesthesia and the lowest Sa_{O_2} recorded during each of these events.

Statistical significance ($P < 0.05$) was determined using Student's t test, Fisher's exact test and Chi-squared test, as appropriate.

RESULTS

Airway complications occurred more frequently in children who received isoflurane than in the halothane group. Coughing and breath-holding were most common, followed by stridor and salivation (table II).

Reductions in Sa_{O_2} occurred during induction of anaesthesia with isoflurane, but not with halothane. Sa_{O_2} values less than 95% were observed in 14 children, and in five of these were less than 80% (table III). All the children receiving halothane had Sa_{O_2} values of 95% or greater.

In the children who received isoflurane, minimum Sa_{O_2} values less than 95% occurred most frequently with breath-holding, salivation, laryngospasm and cyanosis, but less commonly with coughing and stridor (table IV).

Induction of anaesthesia was significantly prolonged with isoflurane compared with halothane (table V).

DISCUSSION

Substantial reductions in Sa_{O_2} occurred during induction of anaesthesia in more than 50% of the children who received isoflurane; Sa_{O_2} was largely unaltered during the use of halothane. The decreases in Sa_{O_2} occurred during airway complications.

It is known that the pungency of isoflurane increases airway irritability and in the present study the increased incidence of airway complications is similar to that found by Fisher and colleagues [4] and Pandit, Stende and Leach [5]. Although McAteer and his colleagues [1] believe that these are of little clinical significance, it is clear that decreases in Sa_{O_2} can occur frequently with salivation and breath-holding. As expected, laryngospasm and cyanosis were associated invariably with reductions in Sa_{O_2}.

Another finding of the study is that induction of anaesthesia was more prolonged with isoflurane than with halothane. This would appear to be at variance with the findings of Gallagher and Black [6], who reported that isoflurane was taken up more rapidly than halothane—a not unexpected finding, as the newer agent has a lower blood/gas partition coefficient [7]. However, in their study, anaesthesia was induced with thiopentone and ventilation was controlled. In contrast, Kingston [8] observed that, in spontaneously breathing children, the uptake of halothane was more rapid than isoflurane—a finding he attributed to the airway irritant effects of the latter agent, breath-holding and coughing reducing the rate of uptake.

Inhalation induction of anaesthesia is suitable particularly for smaller children in whom venous access may be difficult. The use of isoflurane avoids disadvantages of halothane such as arrhythmias [2], myocardial depression [9] and the hazard, albeit remote, of hepatitis [10]. However, the findings of the present study indicate that induction of anaesthesia with isoflurane may be prolonged and that the irritant effects on the airway may interfere with tissue oxygenation. In contrast, halothane produces rapid and smooth induction and Sa_{O_2} concentrations are usually not reduced. Kenna and his colleagues [10] have shown that hepatitis caused by halothane may occur in children and they recommend that repeated exposure to this agent should be avoided if possible. It would seem reasonable to assume that, if isoflurane is used as an alternative to halothane for the induction of anaesthesia in unpremedicated children, a higher incidence of airway complications with associated decreases in Sa_{O_2} may result.

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EFFECT OF DILUTING PROPOFOL ON THE INCIDENCE OF PAIN ON INJECTION AND VENOUS SEQUELAE

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SUMMARY

The effect of diluting propofol in 5% dextrose on the incidence of i.v. injection pain was studied in 100 adult patients. Severe injection pain occurred in 32% (16 patients) who received undiluted propofol, compared with 10% (five patients) who received dilute propofol. We concluded that the dilution of propofol significantly reduced the incidence of severe pain during injection without increasing postoperative venous sequelae.

There have been several studies of the incidence of pain during induction with propofol [1–5]. Pain has been reported in up to 45% of administrations, but adverse venous sequelae have been infrequent [1, 6]. Attempts have been made to reduce pain by injection into a large vein [1] or by using local anaesthetics [2, 3].

This study (approved by the local Ethics Committee) investigated injection pain and venous sequelae when propofol diluted with an equal volume of 5% dextrose was injected into a vein on the dorsum of the hand. Dextrose 5% was chosen as the diluent after discussions with the manufacturer.

METHODS AND RESULTS

We studied 100 adult male or female patients (ASA grades I and II) younger than 70 yr who were scheduled to undergo elective or emergency surgery. Patients with existing signs of venous inflammation were excluded, as were those who had received analgesics in the preceeding 24 h. All patients were premedicated with temazepam 20 mg by mouth. None was told that we were either assessing or expecting injection pain.

In the anaesthetic room, a 22-gauge cannula (Venflon, Viggo) was placed in a vein on the dorsum of one hand through an intradermal bleb of 1% lignocaine. Patients were allocated randomly to two groups: in group I anaesthesia was induced with undiluted propofol 10 mg ml^{-1} injected at a rate of approximately 1 ml s^{-1}; in group II, anaesthesia was induced with propofol freshly diluted to 5 mg ml^{-1} with 5% dextrose injected at a rate of approximately 2 ml s^{-1}. The time from the start of injection to loss of verbal contact and the dose of drug administered were recorded.

During the injection the patient was asked: "is this comfortable?". If the response was negative, the patient was asked, "Does it hurt a little or a lot?" An independent assessor (who was unaware of the propofol formulation) recorded the injection as having caused no pain, moderate pain, or severe pain.

Additional drugs used during maintenance of anaesthesia were injected into the contralateral arm. The cannula through which induction agents were administered was removed after 30 min and the injection site dressed with a dental roll and tape.

Inspection of the injection site was carried out immediately after operation and at 24 h. After the 24-h inspection, each patient was given a questionnaire with the questions: "Does the vein feel tender?". "Does it look red?" and "Does it feel hard or ropey?" to be answered at 4, 8 and 12 days after operation. The questionnaires were returned by post.

There were 32 females and 18 males in group I; 44 were ASA I; mean age was 35.4 (SD 14.1) yr and mean weight 66.6 (11.7) kg. Group II comprised 33 females and 17 males; 44 were ASA I;

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TABLE I. *Incidence of injection pain in patients receiving undiluted (group I) and diluted (group II) propofol. Difference between the two groups significant at P < 0.02 (Chi-squared test)*

Concentration of propofol	No pain on injection	Moderate pain on injection	Severe pain on injection
Undiluted (10 mg ml^{-1})	25	9	16
Diluted (5 mg ml^{-1})	38	7	5

mean age was 41.0 (15.8) yr and mean weight 63.6 (11.2) kg. Mean time from premedication to induction was 89.5 (45.6) min for group I and 108.8 (64.7) min for group II. There was no significant difference between the two groups in any of these variables.

For induction of anaesthesia, group I received a mean (SD) propofol dose of 2.47 (0.36) mg kg^{-1} at 9.8 (1.64) mg s^{-1} and group II received 2.23 (0.31) mg kg^{-1} at 8.2 (1.4) mg s^{-1}. The rates of delivery were significantly different ($P < 0.001$, Student's t test). The mean induction time was 16.9 (3.7) s in group I and 17.8 (5.4) s in group II (ns).

Pain on injection experienced by the patients is shown in table I.

At the 24-h inspection, three patients in group I had a tender vein; in group II one had erythema and two had a tender vein. From the questionnaires (87% were returned), one patient in group I and one in group II reported "hardness" of the vein after 4 and 8 days, respectively, with redness and tenderness. Both these patients had a normal clinical assessment of the injection site at 24 h. They were asymptomatic by 12 days. There were no significant differences in venous sequelae at any time between the two groups (χ^2 test).

COMMENT

The difference in the rate of delivery of propofol may be accounted for by the need to use more than one 20-ml syringe in some of the group II patients. However, there was no significant effect on induction time, which was the period during which the patients were likely to experience any pain.

There was a significant difference between the groups in relation to injection pain (table I). Almost all of this significance resides in the difference in incidence of severe pain: 32% in group I compared with 10% in group II. The genesis of pain after injection of propofol may involve the activation of pain mediators such as kininogens following exposure of the vein wall to the drug [4]. A mechanism such as this may explain both the inter-individual differences observed and attenuation of pain by dilution.

Although this hypothesis may explain partly the reduction in severe pain in group II, it does not account fo the similar incidence of moderate pain in both groups. Our experimental design attempted to match the delivery rate of propofol (mg s^{-1}) in the two groups and this resulted in visible venous distension during induction in some of the patients in group II. This may have contributed to the incidence of moderate pain. It is possible that a slower rate of injection of dilute propofol might be effective in diminishing moderate pain.

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COMPARISON OF CONTINUOUS PARAVERTEBRAL AND EXTRADURAL INFUSIONS OF BUPIVACAINE FOR PAIN RELIEF AFTER THORACOTOMY

P. J. MATTHEWS AND V. GOVENDEN

SUMMARY

Pain was controlled in 20 post-thoracotomy patients using a continuous infusion of 0.25% bupivacaine through an extradural or paravertebral catheter. Both techniques provided good analgesia. Hypotension and urine retention occurred significantly less frequently in the paravertebral than in the extradural group.

Relief of post-thoracotomy pain is beneficial to patients, providing comfort and facilitating physiotherapy and effective expectoration. Continuous extradural analgesia for relief of postoperative pain [1,2] carries two common complications: hypotension and urine retention. Paravertebral analgesia has been rediscovered [3] and recently refined [4]. The aim of this study was to compare the efficacy of continuous infusions of local anaesthetic drugs by these two routes in controlling post-thoracotomy pain.

METHOD AND RESULTS

Hospital Ethics Committee approval and written, informed patient consent was obtained for the investigation. We studied 20 patients undergoing thoracotomy and pulmonary resection. Five patients underwent pneumonectomy: three in group A; two in group B. Three patients underwent lobectomy: two in group A; one in group B. Twelve underwent wedge resection. Thoracotomy was performed via the fifth rib and chest drains inserted between the 9th and 10th or 10th and 11th ribs. The patients' ages were in the range 45–70 yr and their weights 47–83 kg. There were no significant demographic differences between the groups.

All patients received a standard general anaesthetic including papaveretum 0.3 mg kg^{-1}. Before wound closure, patients were allocated randomly to group A (paravertebral) or group B (extradural). In group A a paravertebral catheter was inserted at the T4/5 level using a method described previously [4]. In group B after wound closure, an extradural catheter was inserted at the same vertebral level. Catheter placement was satisfactory in all patients. A 10-ml bolus of plain 0.25% bupivacaine was given through the catheters before antagonism of residual neuromuscular blockade and extubation, and an infusion commenced at 5 ml h^{-1}, adjusted subsequently to 3–10 ml h^{-1} to maintain analgesia in the dermatomes T5–12. Analgesia was unilateral in all patients in group A, and bilateral in all in group B.

Systolic arterial pressure and urine output were recorded hourly. We defined hypotension as a decrease in systolic arterial pressure more than 30 mm Hg from the preoperative value, and urine retention as significant if catheterization was necessary. A 10-cm linear analogue pain scale was completed 4, 12 and 24 h after operation and the spread of analgesia assessed using an ethyl chloride spray. The patient's physiotherapist indicated if analgesia was adequate for co-operation with physiotherapy and effective expectoration.

One patient was withdrawn from group B because hypotension persisted despite an infusion of colloid and ephedrine 10 mg i.v. The data presented are from the remaining 19 patients.

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TABLE I. *Linear analogue pain scores (mean (SD)), urine retention and hypotension in the groups receiving paravertebral or extradural infusions of bupivacaine.* n = *No. patients*

	Group A Paravertebral	Group B Extradural	P
Pain score (cm)			
4 h	1.3 (1.1) ($n = 10$)	1.3 (1.2) ($n = 9$)	ns
12 h	1.4 (1.5) ($n = 10$)	1.3 (0.9) ($n = 9$)	ns
24 h	0.6 (0.6) ($n = 7$)	1.2 (0.8) ($n = 9$)	ns
Urine retention	1/10	6/9	< 0.01
Hypotension	0/10	6/9	< 0.01

Parametric data were analysed using Student's *t* test and non-parametric data using the Mann–Whitney and Chi-square tests.

Pain scores were similar in the two groups (table I) and all patients in group A, and all but one patient in group B, were able to co-operate with physiotherapy and expectorate adequately.

No patient in group A, but six in group B became hypotensive ($P < 0.01$); one patient in group A and six in group B suffered from urine retention ($P < 0.01$) (table I).

Mean infusion rates were similar in the two groups: group A 0.25 mg kg^{-1} h^{-1}; group B 0.26 mg kg^{-1} h^{-1}. No patient developed clinical evidence of bupivacaine toxicity.

COMMENT

Thoracic extradural infusions of bupivacaine provide excellent post-thoracotomy analgesia, but are associated with a high incidence of hypotension and urinary retention because of bilateral sympathetic blockade [1,2]. The ideal concentration of bupivacaine and ideal infusion rate to optimize pain relief and minimize these side effects have not yet been established, although concentrations of 0.125–0.375% are effective [1,2]. In the first 24 h after surgery, the patients with extradural analgesia required larger volumes of i.v. colloid to maintain a normal arterial pressure, which may have increased the incidence of urine retention. One patient given an extradural infusion was withdrawn from the study because of persistent hypotension.

Paravertebral blockade is predominantly unilateral and a lower incidence of side effects would be expected, as we found in this study. There was no evidence of contralateral blockade from paravertebral injection, confirming previous findings [5]. The rate of infusion of bupivacaine was adjusted according to dermatomal sensory levels, assessed using the cold stimulus of an ethyl chloride spray. This does not test for complete analgesia, but proved to be an effective assessment of spread for this purpose. All patients were nursed in a semi-recumbent position and we found a tendency for lower dermatomes to become anaesthetic as patients became more mobile and assumed a more erect posture. This effect was more evident in the paravertebral group. Patients were nursed on a high dependency unit and the bupivacaine infusions were discontinued before transfer to the postoperative ward.

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OXYGEN DESATURATION FOLLOWING SEDATION FOR REGIONAL ANALGESIA

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SUMMARY

Moderate to severe arterial oxygen desaturation (Sa_{O_2} 75–88%) occurred in three of four patients who were given sedation during regional conduction block without the administration of oxygen. No desaturation occurred in six patients given oxygen 2 litre min^{-1} via a nasal catheter during similar procedures. It is concluded that patients undergoing regional conduction block with concurrent sedation should receive additional oxygen routinely unless a pulse oximeter is available for monitoring.

Many patients, especially those in certain "high risk" groups, undergo operative procedures under regional analgesia in the belief that this approach is safer than general anaesthesia; this is particularly the case for patients with coexistent lung disease. During the procedure, sedation is often provided with an i.v. agent, for example midazolam, diazepam or propofol. It seems (from personal observation) that administration of oxygen to the patient in this situation is not routine in current European practice. There is only equivocal guidance on this topic from reference works on local anaesthesia [1, 2] and most do not mention the use of oxygen, except to treat the complications of regional anaesthesia [3–5].

We decided to study the effects of sedation with midazolam on oxygen saturation (Sa_{O_2}) as measured by pulse oximetry in patients undergoing surgery under regional conduction block.

PATIENTS AND METHODS

A study was planned of 100 patients aged 20–85 yr and in ASA categories I–III. Patients were randomly allocated to one of two groups according to the last digit of the hospital number: the first group (odd digit) received oxygen 2 litre min^{-1} via a 12-French gauge nasal catheter (without foam nostril plug) during surgery, the second group (even digit) received no additional oxygen unless Sa_{O_2} decreased to less than 90%. All patients underwent surgery under regional conduction block in combination with sedation using increments of midazolam 1.0–2.5 mg i.v. as required. The level of sedation was controlled such that the patient was drowsy but aroused easily and capable of communication. Upper airway patency was maintained at all times. Sa_{O_2} was monitored continuously during the procedure using a prototype Datex Satlite pulse oximeter. The standard adult finger probe on a randomly selected finger was applied according to the manufacturer's instructions. Monitoring was commenced after the patient had been positioned for induction of the block, and continued until the end of the surgical procedure.

Unfortunately, we felt compelled to abandon this study after only 10 patients had been investigated, as a result of profound reductions in Sa_{O_2} which occurred in some patients breathing only air. In all patients given supplementary oxygen, Sa_{O_2} remained greater than 90% throughout the procedure. A brief résumé follows of the three patients in whom desaturation occurred.

Patient 1

A 63-yr-old man, ASA category I, underwent elective total hip replacement. Clinical history and examination, laboratory investigations, chest x-ray and ECG were normal. Arterial pressure

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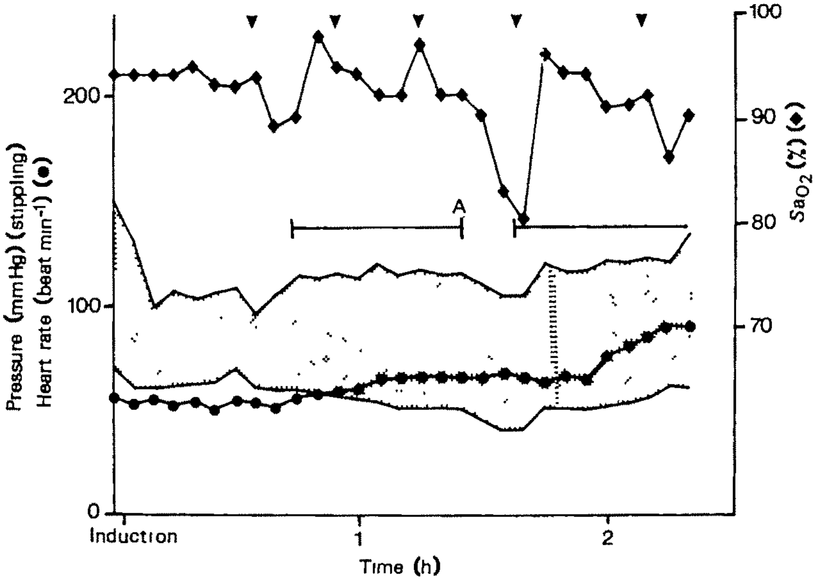

FIG. 1. Course of anaesthesia in patient 1. Incremental doses of midazolam are shown by arrows. The horizontal bars indicate administration of oxygen 2 litre min^{-1}; at point A the patient removed the oxygen catheter.

was 140/90 mm Hg. The patient refused premedication. Extradural anaesthesia was administered via the L3–4 space using 2.0% mepivacaine 20 ml with adrenaline 1:200000, producing a bilateral sensory loss to T6. No extension of the block occurred during surgery. Sedation was provided with an initial dose of midazolam 2.5 mg i.v., followed by increments of 1 mg i.v. as required (fig. 1—arrows). After the first dose the patient was sleepy but rousable; Sa_{O_2} decreased to less than 90% and oxygen 2 litre min^{-1} was administered via a nasal catheter. Sa_{O_2} improved to an acceptable value. However, following each subsequent dose of midazolam a reduction in Sa_{O_2} occurred, although not to values below 90%. At point A in figure 1, the patient removed the oxygen catheter, whereupon Sa_{O_2} decreased precipitously. The oxygen catheter was replaced in his nose, resulting in an immediate improvement in Sa_{O_2}.

Patient 2

A 70-yr-old man, ASA category I, underwent transurethral prostatectomy. Arterial pressure was 140/85 mm Hg. Laboratory analyses, ECG and chest x-ray were within normal limits. Premedication with temazepam 20 mg by mouth was given 2 h before surgery; the patient arrived in the anaesthetic room awake and co-operative. Analgesia was achieved with hyperbaric 0.5% bupivacaine 20 mg injected intrathecally at L4–5 with the patient sitting. A bilateral sensory block to L1 was produced which remained stable during the operation. Sedation was provided with an initial dose of midazolam 2.5 mg i.v., followed by increments of 1 mg i.v. An initial decrease in systolic arterial pressure to less than 100 mm Hg accompanied induction of the block, despite a preload with Hartmann's solution 500 ml (fig. 2). Superimposed upon this, the first dose of midazolam (arrows, figure 2) was associated with a reduction in Sa_{O_2} to less than 90%. The patient refused additional oxygen, but both arterial pressure and Sa_{O_2} increased to acceptable values after the administration of ephedrine 10 mg i.v. All subsequent doses of midazolam, with the exception of the third, also were associated with transient reductions in Sa_{O_2} to less than 90%. However, only the second and third doses of midazolam were associated with further reductions in systolic arterial pressure, although on these occasions not to less than 100 mm Hg.

Patient 3

A 59-yr-old man, ASA category I, underwent urethroplasty. Laboratory analyses, ECG and chest x-ray were within normal limits. Premedication consisting of diazepam 10 mg and

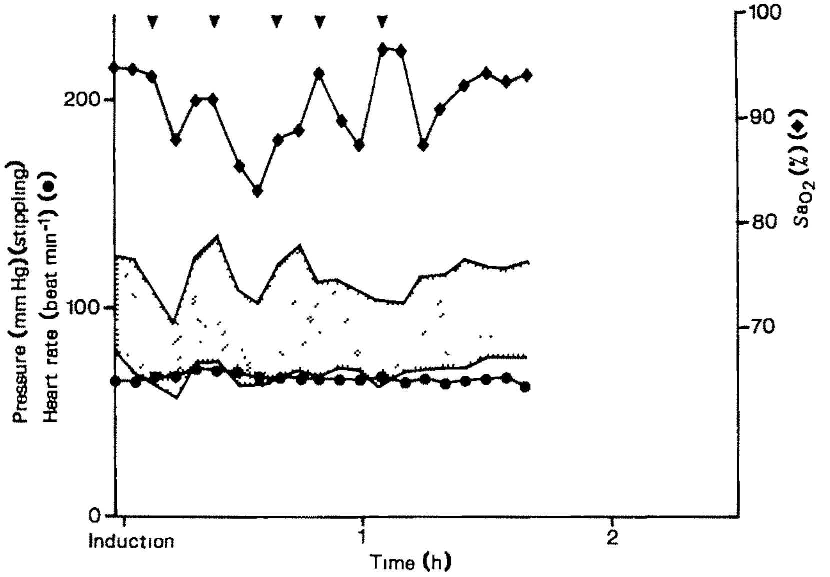

FIG. 2. Course of anaesthesia in patient 2. Incremental doses of midazolam are shown by arrows.

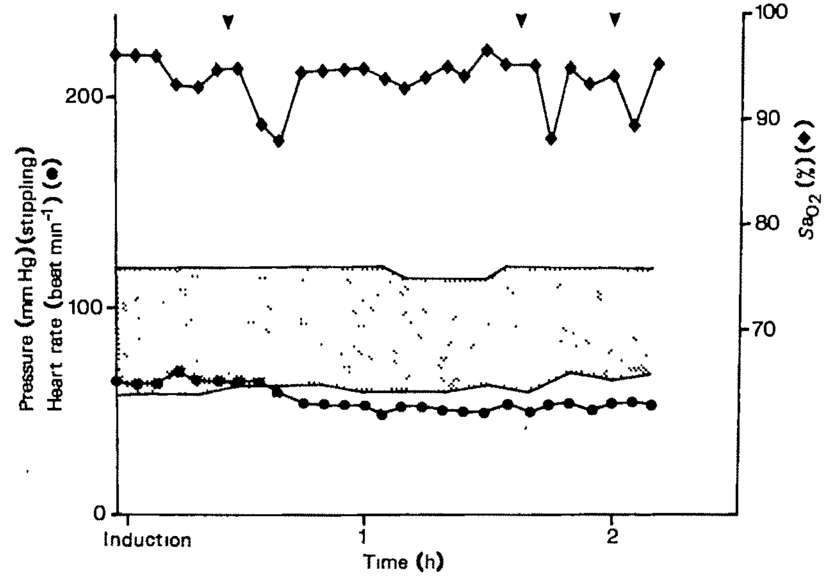

FIG. 3. Course of anaesthesia in patient 3. Incremental doses of midazolam are shown by arrows.

droperidol 2.5 mg was given by mouth 2 h before the procedure; he arrived in the anaesthetic room awake and co-operative. Analgesia was produced with hyperbaric bupivacaine 20 mg injected intrathecally at the L2–3 space with the patient sitting. A bilateral sensory block to T10 was produced which remained at this level throughout the procedure. Sedation was provided with an initial dose of midazolam 2.5 mg i.v., followed by increments of 1 mg i.v. as required. Figure 3 details the course of this anaesthesia, showing reductions in Sa_{O_2} in response to administration of midazolam, not associated with changes in arterial pressure or heart rate.

DISCUSSION

These patients illustrate a potential danger during regional conduction blockade combined with sedation if additional oxygen is not administered to patients during surgery.

There are three factors which may interact to cause the observed reduction in Sa_{O_2}. First, compensatory reflex vasoconstriction in areas not subject to sympathetic blockade may result in a reduction in Sa_{O_2}, the degree depending upon the performance of the individual pulse oximeter in the face of reduced perfusion at the measuring site. The Satlite produces a pulse waveform derived from the light absorption curve, but no variation in the amplitude of the waveform was seen during the cases reported. Compensatory reflex vasoconstriction should persist for the duration of the block, while the phenomena reported here were transient.

A second possible factor is hypoventilation resulting from sedation. Although we did not assess formally the degree of ventilation, all patients were easily rousable and had a patent upper airway and an adequate rate of ventilation. However, hypoventilation would explain the transient reductions in Sa_{O_2} occurring in the absence of cardiovascular changes, seen in all three patients reported here.

Third, ventilation–perfusion mismatch may occur as a result of a combination of relative hypovolaemia, depression of cardiac output and reduction in FRC consequent upon the supine position. This would result in a reduction in Sa_{O_2}, and may explain the initial decreases in both Sa_{O_2} and arterial pressure in patient 3. This may be the same phenomenon of intrapulmonary shunting described during general anaesthesia [6, 7].

The question as to the value of Sa_{O_2} at which intervention becomes necessary is unanswered [8–10], and has been complicated by the recent demonstration that the pulse oximeter reading is not dependent solely upon pulsation within the arteriolar side of the circulation [11]. Further investigation, combined with adequate statistical analysis [12] is required before conclusions can be drawn on accurate measurements of Sa_{O_2} based upon data obtained from a pulse oximeter. Following a study of 150 "normal" individuals (Authors' unpublished observations), we regard a lower limit for a pulse oximeter reading of 90% as being practicable in most circumstances.

We conclude that major regional conduction blockade, combined with sedation, should not be used without the administration of additional oxygen unless a pulse oximeter is available.

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PANCURONIUM ALLERGY: A CASE REPORT

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SUMMARY

A case of anaphylactic shock to pancuronium bromide is described in which a type I immunological reaction occurred. A 33-yr-old male anaesthetist, with no family or personal history of allergy, collapsed soon after induction of anaesthesia. The drugs used included fentanyl, droperidol, thiopentone and pancuronium. Diffuse erythema occurred, with probable cardiac arrest. The patient was treated with cardiac massage, sympathomimetics and cortisone, and made a complete recovery. Examination (skin tests, passive transfer according to Prausnitz and Küstner, in vitro *lymphocyte transformation test, total IgE assay) revealed that the allergic reaction was to pancuronium bromide.*

Because of increased use of synthetic neuromuscular blocking drugs, there has been an increase in the number of reported cases of hypersensitivity reactions, caused partly by immunological mechanisms (reaginic) [1] and in the majority of cases by non-immunological factors (release of histamine, complement activation etc.) [2, 3].

Pancuronium is well tolerated, but cases of undesirable secondary reactions have been reported [2–4].

We report here a case of anaphylactic shock caused by pancuronium bromide in which a type I immunological mechanism (IgE mediated) was implicated.

CASE REPORT

A 33-yr-old male anaesthetist with no family or personal history of allergy, had twice undergone surgery under general anaesthesia. An appendicectomy was performed at age 11 yr and the removal of a salivary gland at age 28 yr (table I). The drugs administered during the first operation remain unknown, but during the second operation the patient received thiopentone, suxamethonium, tubocurarine, halothane, neostigmine and atropine, without any complications.

On the present admission the patient was scheduled to undergo cholecystectomy. Premedication comprised diazepam and atropine and anaesthesia was induced with fentanyl–droperidol and thiopentone followed by pancuronium i.v. Immediately after the administration of these drugs, the patient developed cardiovascular collapse and diffuse erythema, with probable cardiac arrest. Cardiac massage was performed immediately and resuscitation instituted with colloids i.v. (gelatins) and methylprednisolone, atropine, metaraminol, adrenaline, bicarbonate, dopamine and mannitol were administered. The patient responded to this treatment and made a good recovery. Surgery was postponed.

Fifteen days after the episode, the case was brought to our attention and we performed the following tests: skin tests, passive transfer according to Prausnitz and Küstner [5] (the patient's serum was screened for hepatitis antigen and antibody, syphilis and AIDS by the use of HTLV-III antibody), lymphocyte *in vitro* transformation test and total IgE radioimmunoassay (Prist-Pharmacia).

Skin tests were performed with intradermal (i.d.) injections of appropriate concentrations of atropine, diazepam, tubocurarine, thiopentone, enflurane, fazadinium, pancuronium and suxamethonium (table II). Negative results were obtained for all the drugs used, with the exception of pancuronium bromide.

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TABLE I. *Drugs administered to the patient in the various general anaesthesias*

1st Operation	2nd Operation	3rd Operation (Anaphylactic shock)	4th Operation
Unknown	Atropine	Atropine	
	Suxamethonium		Suxamethonium
	Thiopentone	Thiopentone	Thiopentone
		Fentanyl–droperidol	Fentanyl–droperidol
		Pancuronium	
		Diazepam	
	Halothane		
	Neostigmine		
	Tubocurarine		
			Nitrous oxide

TABLE II. *Drugs used for skin tests (prick and intradermal), and reactions*

Drug (dilution)	Reaction
Atropine (10^{-2})	–
Diazepam (10^{-3})	–
Tubocurarine (10^{-5})	–
Thiopentone (10^{-2})	–
Enflurane (undiluted)	–
Fazadinium (10^{-5})	–
Suxamethonium (10^{-4})	–
Pancuronium (10^{-4})	++

An injection of pancuronium 0.05 ml highly diluted to 10^{-12} was followed by the appearance of a 1-cm diameter weal surrounded by a 4-cm diameter erythematous halo. A similar i.d. injection to 10 healthy control subjects was negative; this test was performed to exclude the possibility that the positive reaction was caused by histamine release [3].

Passive transfer according to Prausnitz and Küstner [5] was carried out. This test is used to confirm the positive nature of a skin test by transferring the reaction to a volunteer. The aim is to induce the specific IgE (if present in the examined serum) to fix on the surface of the skin mast cell. The further administration of the allergen in the same site causes an antigen–antibody reaction, resulting in a weal and flare. The patient's serum (fresh and heated to 56 °C for 3 h) was injected i.d. (0.1 ml) in several areas of the volar surface of the forearm in two members of the patient's family. After 4 h and 48 h, the two family volunteers were injected i.d. with pancuronium 0.1 ml (1:10000), suxamethonium, tubocurarine and with normal saline in the same sites as the preceding inoculations of serum. The 4-h interval was used to reveal skin-sensitizing IgG ("short term sensitizing antibodies"); the 48-h interval was used to reveal IgE. Readings after 4 h were negative, whereas after 48 h a weal and flare reaction was evident only in the site, pretreated with unheated serum, to which pancuronium was subsequently injected.

The *in vitro* lymphocyte transformation test was carried out using a radioisotopic technique using thymidine 2-C^{14} (Radiochemical Centre Amersham) [6]. A stimulation index of 3 was considered significant. The stimulation index is calculated by dividing the number of counts per minute from cultures with the antigen, by number of counts per minute from the non-stimulated control cultures. In this test the following antigen solutions were used: pancuronium and suxamethonium (0.02 ml of solutions diluted by 10^{-3}, 10^{-4} and 10^{-5}). These non-lymphotoxic doses had been determined previously by culturing the lymphocytes in the presence of 0.05 ml ml^{-1} of rehydrated BACTO-Phytohaemagglutinin M Difco (PHA) culture with various doses of the drugs for 4 days. Control cultures were prepared also with no antigen, or with the addition of 0.2 ml of a solution of PHA. Significant increase in lymphocyte proliferation was observed in cultures with pancuronium (stimulation index = 5.7). No significant increase in thymidine incorporation was observed in the cultures with suxamethonium.

Subsequently, the patient underwent uneventful cholecystectomy with a drug regimen as shown in table I.

DISCUSSION

The results obtained from our patient confirm an immunological pathogenesis mediated by IgE (passive transfer was prevented by heating the serum for 3 h at 56 °C: IgE are antibodies which denature at high temperatures).

Minimal concentrations of pancuronium (10^{-12}) produced positive skin reactions in the patient, with no responses in the 10 control subjects: this excludes histamine release as a mechanism. On the other hand, the Prausnitz and Küstner test was positive, after 48 h, only with the non-heated serum, demonstrating the presence of long term sensitizing antibodies, involved in type I immunoreactions.

The positive lymphocyte transformation test demonstrated the presence of memory T cells capable of recognizing the antigen and of proliferating. This indicates that the patient's immune system had already been in contact with the antigen and had induced an immunological response. With radioimmunoassay for total IgE (Prist-Pharmacia), a result within normal limits (64 ku. litre^{-1}) was obtained for our patient. This is compatible with drug allergy [7].

It is not clear how the patient was sensitized to pancuronium. The drugs used in his first anaesthesia remain unknown and is possible that pancuronium was used. Alternatively, it is possible that sensitization occurred transcutaneously (or even by inhalation) as the patient worked as an anaesthetist. Cross-sensitivity with other neuromuscular blocking drugs may be excluded [8] as the testing was negative for both tubocurarine and suxamethonium. Furthermore, the patient underwent a subsequent general anaesthesia with suxamethonium, without incurring problems. For this reason, the quaternary ammonium group cannot be considered responsible for the drug allergy [9].

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HEART BLOCK FOLLOWING PROPOFOL: A CASE REPORT

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SUMMARY

We report two cases of ventricular arrest with persisting atrial activity in association with propofol anaesthesia. In both cases, anticholinergic agents corrected the arrhythmia. It is recommended that anticholinergic drugs be given routinely when propofol is used in association with vagal stimulants.

Propofol is a new anaesthetic agent with a smooth and rapid onset of action similar to that of thiopentone [1], but with a very fast clearance from blood [2] and, consequently, a short duration of action. It also appears to have a low potential for histamine release [3] and does not cause suppression of steroid synthesis [4]. However, bradycardia [5] and hypotension [6] have been described as complications following use of the agent, but heart block has not been documented. We report two cases of ventricular asystole apparently with total heart block; in one patient propofol was used as an induction agent and in the other, continuous i.v. anaesthesia with propofol was used.

CASE REPORTS

Patient 1

The patient was an obese 54-yr-old female who weighed 98 kg, presenting for total abdominal hysterectomy and bilateral salpingo–oophorectomy. Significant previous medical history included hypertension for which she was receiving sotalol 80 mg day^{-1} and hydrochlorothiazide 12.5 mg day^{-1}. She also had a hiatus hernia. Preoperative cardiovascular data included arterial pressure of 150/90 mm Hg, a regular heart rate of 72 beat min^{-1} and an ECG which showed a left ventricular strain pattern, but no conduction defects. The remainder of the clinical examination was normal. Preoperative investigations included a chest x-ray, and haemoglobin, urea and electrolyte estimations, which were all normal. For the calculation of drug doses a lean body mass of 80 kg was assumed. Anti-hypertensive medication was continued on the morning of surgery, and premedication consisted of papaveretum 10 mg and promethazine 25 mg i.m. 1 h before operation.

In the operating theatre the heart rate was 83 beat min^{-1} and arterial pressure 140/80 mm Hg. ECG leads were attached and arterial pressure was monitored every 1 min during the induction sequence using a non-invasive automatic device. In view of her hiatus hernia, a rapid sequence induction was performed. Following pre-oxygenation, anaesthesia was induced with propofol 200 mg given over 30 s, followed by suxamethonium 80 mg. Cricoid pressure was applied and, after fasciculations had ceased but before intubation, it was noticed that although there were regular P-waves with a rate of 70 min^{-1}, there were no QRS complexes, and no pulse could be felt. Tracheal intubation was performed, and QRS complexes reappeared spontaneously with normal configuration and persisted for several normal beats. Manual ventilation of the lungs was instituted with 100% oxygen and 3% enflurane introduced. Within a few seconds, QRS complexes again disappeared, although P-waves persisted. Following 10 P-waves, normal QRS complexes returned, with a good output. A third similar episode occurred after an interval of a few seconds of normal sinus rhythm. Atropine 0.6 mg was administered i.v., and no further episodes occurred. This sequence of events took place over the

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space of 1 min, and no arterial pressure recordings were made at this time. The next arterial pressure recording taken immediately after the atropine was given was 120/70 mm Hg, with a heart rate of 70 beat min^{-1}. Surgery proceeded uneventfully, and the patient recovered from the anaesthetic normally. A post operative ECG was identical to the preoperative tracing.

Patient 2

This patient was a 46-yr-old male with proven malignant hyperpyrexia susceptibility scheduled to undergo elective cholecystectomy. Preoperative evaluation included a full blood count, chest x-ray, ECG and urea and electrolyte measurements, all of which were normal. Preoperative arterial pressure was 130/90 mm Hg and heart rate 80 beat min^{-1}. Before induction, a radial arterial and a central venous catheter were inserted, and ECG leads attached. A halothane-free machine was used, and a continuous propofol anaesthetic technique adopted, with an induction dose of 180 mg and boluses of propofol 25–40 mg given as indicated by increases in heart rate or arterial pressure. Neuromuscular blockade was achieved with alcuronium 20 mg and controlled ventilation was maintained with 50% oxygen in nitrous oxide. The procedure was uneventful, and at the end of surgery residual neuromuscular blockade was antagonized with neostigmine 2.5 mg and glycopyrrolate 0.4 mg. Within a few seconds, QRS complexes disappeared, although P-waves persisted at an unchanged rate; arterial pressure was unrecordable and the patient began to sweat profusely. A further glycopyrrolate 0.4 mg was administered, and QRS complexes returned immediately with restoration of a normal arterial pressure. Intermittent episodes of heart block occurred with ventricular standstill of brief duration, for the next 30 min, but thereafter no further episodes were seen. The patient was monitored for the next 24 h and remained stable. Subsequently, further surgery was required for a wound dehiscence, and this was managed with regional blockade and was uneventful.

DISCUSSION

The cardiovascular effects ascribed to propofol include hypotension resulting from a combination of decreased systemic vascular resistance and a reduced cardiac output, and minimal changes in heart rate, although occasional bradycardia, responsive to atropine, has been described [4, 6]. Continuous propofol anaesthesia has been administered in combination with intermittent doses of suxamethonium, without serious bradycardia being reported, although the patients were premedicated with atropine [7]. Arrhythmias have not been described previously, but there has been a report of cardiac arrest following the use of propofol. In this patient, the arrest responded rapidly to the administration of atropine and a brief period of cardiac massage [8]. Another patient in this report had a severe bradycardia which responded to atropine.

Both of the patients described here received cholinergic stimuli before the onset of arrhythmia. In the first, suxamethonium was administered without an anticholinergic before intubation, and in the second neostigmine was given accompanied by a relatively small dose of glycopyrrolate. In both patients the ventricular arrest responded to administration of an anticholinergic agent, suggesting that vagal stimulation was responsible at least partly for the events. However, if a vagally mediated cause for the ventricular arrests is to be postulated, it is surprising that P-waves continued unchanged in both cases.

Both patients had some cardiovascular disturbance. The first patient was hypertensive, receiving beta-blockers, with some evidence of ventricular strain. The second patient suffered from malignant hyperthermia susceptibility, and may therefore have had underlying myocardial abnormality, although there was no clinical or ECG evidence for this. The safe use of propofol in MH has been described recently [9].

There is some evidence that propofol may depress the SA node directly (K. J. Hopkins, personal communication), but no evidence at present that the drug affects atrioventricular conduction. The explanation for the events observed therefore remains obscure, but it would seem advisable at present to recommend that an anticholinergic drug be administered whenever propofol is given in combination with potential cholinergic stimulant agents. This is advisable particularly if the patient is also receiving a beta-blocker.

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PROFOUND INTRAOPERATIVE ATELECTASIS

S. I. SAMUELS AND J. B. BRODSKY

SUMMARY

Severe intraoperative hypoxaemia occurred in a previously healthy 19-yr-old accident victim. Although rare, major lung collapse secondary to mucous plugging should be considered in the differential diagnosis of intraoperative hypoxaemia, particularly following major trauma.

Although pulmonary atelectasis is a common postoperative event, major intraoperative lung collapse is very rare. We report a case of right middle and lower lobe collapse occurring secondary to mucous obstruction of the airways. A review of the literature suggests that this complication appears to be associated with surgical patients following major trauma. Although uncommon, massive atelectasis should be considered in the differential diagnosis of intraoperative hypoxaemia in trauma patients.

CASE REPORT

The patient was a 19-yr-old male who was found unconscious beneath his motorcycle. On admission to another hospital, he had regained consciousness. His arterial pressure was 100/70 mm Hg and heart rate 100 beat min^{-1}. On physical examination, a marked deformity of the left thigh was noted. Shortly after admission the patient became disorientated and appeared to have difficulty breathing. Neuromuscular blockade was performed, the trachea intubated and mechanical ventilation begun. An x-ray of the left femur revealed a fracture. Chest x-ray revealed possible widening of the mediastinum. I.v. fluid resuscitation was begun and the patient transferred to our hospital for further treatment.

On admission, a computerized tomogram scan of the head revealed a basilar skull fracture and evidence of intracerebral haemorrhage in the posterior horn of the left lateral ventricle. Arterial blood-gas analysis showed pH 7.43, Pa_{CO_2} 3.3 kPa and Pa_{O_2} only 50.3 kPa during artificial ventilation of the lungs with 100% oxygen.

The next day in the Intensive Therapy Unit (ITU), oxygen saturation (Sa_{O_2}), measured by pulse oximetry, decreased from 99% to 90% ($FI_{O_2} = 0.6$). Chest x-ray revealed complete collapse of the right upper and lower lobes. Fibreoptic bronchoscopy was performed at the bedside. The major airways on the left appeared normal. The bronchi to the right upper and lower lobes were obstructed completely by thick mucous plugs; pulmonary toilet and suction through the bronchoscope cleared the airways. The patient tolerated the procedure and the trachea was extubated soon afterwards.

The following day, the patient underwent intramedullary nailing of the femur. He was premedicated with midazolam 2 mg i.v. A cannula was placed in the right radial artery and two i.v. cannulae were inserted. Monitoring included use of electrocardiogram, mass spectrometry, automated arterial pressure device, oesophageal stethoscope and a pulse oximeter.

Anaesthesia was induced with sodium thiopentone 300 mg i.v., and tracheal intubation was facilitated with suxamethonium 100 mg i.v. Similar breath sounds were heard in both lung fields following insertion of the tracheal tube. General anaesthesia was maintained with 66% nitrous oxide and isoflurane in oxygen and supplemented with fentanyl i.v. Neuromuscular blockade was achieved with pancuronium bromide 3 mg i.v.

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Ventilation was controlled with a tidal volume of 1000 ml at a rate of 6–7 b.p.m. Peak inspiratory pressure was 20 cm H_2O. Following induction of anaesthesia, the patient was placed in the right lateral decubitus position. The chest was again auscultated and breath sounds appeared similar in both lung fields.

Surgery proceeded uneventfully. Approximately 1 h after the induction of anaesthesia, there was a sudden increase in the patient's heart rate from 110 to 150 beat min^{-1}. At the same time Sa_{O_2}, which had been stable at 97%, decreased suddenly to 80%.

Manual ventilation of the lungs was begun. With a tidal volume of 1000 ml the peak inspiratory pressure was 35 cm H_2O. The chest was again auscultated, and there was now a marked decrease in the breath sounds on the right side compared with the left. No wheezing was heard. The tracheal tube was withdrawn 2 cm and suctioned, but no material was obtained. These manoeuvres did not improve the quality of air entry in the right lung and Sa_{O_2} remained at 90% with an FI_{O_2} of 1.0, despite 5 cm of positive end-expiratory pressure. Arterial blood-gas analysis revealed pH 7.29, Pa_{CO_2} 7.5 kPa and Pa_{O_2} 6.5 kPa. The planned operation was abandoned and the patient was returned to the supine position without any improvement in Sa_{O_2}.

In the recovery room chest x-ray revealed collapse of the right middle and lower lobes. He was returned to the ITU, where fibreoptic bronchoscopy was again performed through the tracheal tube. The major airways on the left appeared normal. However, the right middle lobe bronchus and right lower lobe bronchus were obstructed by mucous plugs. These were removed by suction. The patient tolerated the procedure well and post-bronchoscopy chest x-ray revealed full expansion of the right lung. At the end of the procedure oxygen saturation was 100%. The patient's condition continued to improve and he was discharged to the ward several days later.

DISCUSSION

Acute lung collapse during operation is a potentially fatal condition, so early detection is essential. Complete collapse of a lobule, segment, lobe or entire lung may occur from a variety of causes; the resultant extent of hypoxaemia depends on the amount of blood shunted past the collapsed lung tissue. The diagnosis of profound atelectasis may be made by clinical signs of hypoxaemia and decreased or absent breath sounds, and is confirmed by chest x-ray or by bronchoscopy. During anaesthesia the signs of hypoxaemia, tachycardia, cyanosis and tachypnoea may or may not be present and hypoxaemia may be detected by arterial blood-gas analysis or by pulse oximetry.

A number of possible causes were considered for the sudden intraoperative decrease in Sa_{O_2}, the diminished and unequal breath sounds over the right chest, and the low Pa_{O_2} that occurred in our patient during anaesthesia. Movement of the tracheal tube, resulting in an inadvertent left bronchial intubation, pneumothorax and pulmonary aspiration were considered initially. No clinical improvement resulted from withdrawing the tube. Although one would suspect that aspiration at the time of injury resulted in the hypoxaemia observed, no vomitus or foreign material appeared after suctioning through the tracheal tube. A tension pneumothorax was considered, but the relatively low peak inspiratory pressures and the cardiovascular stability without evidence of subcutaneous emphysema made this diagnosis unlikely. The time course and unilateral physical signs argued against fat emboli as the aetiology of hypoxaemia.

Although intraoperative lung collapse in the absence of the more common causes such as aspiration, bronchial intubation and pneumothorax has been reported in the past, no definite cause was discovered in the majority of patients [1–5]. In reviewing the literature we found only two reports, describing a total of four patients in whom mucous plugging on the bronchi was shown to be the sole aetiology of major atelectasis occurring in the absence of the other, more common causes of lung collapse [6, 7]. In three of the four patients, intraoperative lung collapse occurred during orthopaedic surgery following motor vehicle trauma. Thus the combination of recent trauma and surgery may be associated with intraoperative lung collapse from mucous obstruction. Although this is a rare complication, it should be considered in the differential diagnosis of hypoxaemia during trauma surgery.

As intraoperative hypoxaemia can occur from many causes even in healthy patients, the routine use of pulse oximetry is encouraged. Although extremely reliable, the intermittent information obtained from arterial blood-gas analyses results in delay between the time of sampling and corrective action.

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PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

LONDON MEETING

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EFFECT OF DOBUTAMINE INFUSION ON THE ADRENOCORTICAL RESPONSE TO HALOTHANE ANAESTHESIA IN PONIES

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Halothane anaesthesia, without surgery, induces a substantial adrenocortical response in ponies [1]. Halothane-induced hypotension is severe in this species and may be responsible for the adrenocortical response. Dobutamine is often infused to maintain normotension during equine clinical anaesthesia. The present study was designed to investigate if maintenance of normotension with dobutamine infusion during halothane anaesthesia would ameliorate the adrenocortical response.

Six healthy ponies with a previously raised carotid artery were studied. Arterial pressure (AP) was measured from a carotid artery catheter and blood was withdrawn for cortisol assay before anaesthesia (control), at 20-min intervals throughout 2 h of anaesthesia, and during recovery. Anaesthesia was induced with thiopentone and maintained with halothane in oxygen. Dobutamine 1.5–3.5 $\mu g\ kg^{-1}\ min^{-1}$ was infused throughout anaesthesia to maintain AP at preanaesthetic values. Dobutamine was also infused at the same rate for 2 h in six conscious ponies. AP and cortisol concentration were measured at the same intervals.

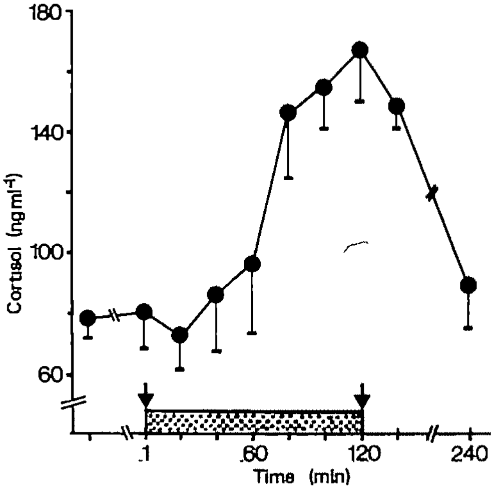

FIG. 1. Cortisol concentration during 20 min of halothane anaesthesia (arrows) with dobutamine infusion (stippling). C = Control.

Dobutamine infusion did not ameliorate the adrenocortical response during halothane anaesthesia (fig. 1). Plasma cortisol concentration increased in a manner similar to that seen with halothane anaesthesia alone [1]. In the conscious group, dobutamine induced a small increase in AP. The control cortisol concentration was greater than in the anaesthetized group, but there was no change during the infusion.

These results demonstrate that, although dobutamine infusion prevented the halothane induced hypotension, it had no effect on the adrenocortical response. This suggests that hypotension is not solely responsible for the response. Alternatively, dobutamine may itself stimulate the pituitary–adrenal axis, although results from the conscious group do not support this.

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COMPARISON OF INCREASES IN END-TIDAL CONCENTRATIONS OF HALOTHANE AND ISOFLURANE IN ELDERLY PATIENTS

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End-tidal concentrations of isoflurane have been shown to increase more rapidly than those of halothane at induction of anaesthesia in young healthy subjects [1, 2]. Ageing, however, causes tissue solubility and cardiorespiratory changes which might alter uptake of volatile agent. This study compared the increase in end-tidal concentrations of isoflurane and halothane in elderly patients.

Twenty-two healthy patients aged between 60 and 80 yr were studied before elective surgery. None had recently received halothane. Informed consent was obtained and approval was given by the local Medical Research Ethical Committee.

After induction of anaesthesia with a sleep dose of thiopentone, pancuronium 0.1 $mg\ kg^{-1}$ and alfentanil 15 $\mu g\ kg^{-1}$, the trachea was intubated and intermittent positive pressure ventilation commenced with 100 % oxygen. Patients were randomly assigned to receive either 0.8 % halothane or 1 % isoflurane which was then added to the inspired gas. Ventilation was adjusted to maintain end-tidal carbon dioxide partial pressure at 4.7 kPa. Inspired (F_I) and end-tidal (F_E) concentrations of volatile agent were measured continuously for 20 min using a Datex Normac CD300 infra-red vapour

TABLE I. *Change (mean (SD)) in ratio of end-tidal to inspired concentration of volatile agent* (FE:FI) *during induction of anaesthesia*

Time (min)	*FE*:*FI* Halothane	*FE*:*FI* Isoflurane
1	0.330 (0.058)	0.398 (0.044)
2	0.358 (0.057)	0.444 (0.038)
3	0.386 (0.059)	0.464 (0.031)
4	0.412 (0.061)	0.480 (0.030)
5	0.432 (0.072)	0.509 (0.027)
7	0.478 (0.070)	0.537 (0.037)
10	0.481 (0.072)	0.569 (0.037)
12	0.500 (0.069)	0.588 (0.044)
15	0.513 (0.068)	0.603 (0.043)
17	0.517 (0.070)	0.611 (0.044)
20	0.532 (0.073)	0.619 (0.051)

analyser. Arterial pressure and electrocardiogram were recorded continuously.

The ratio *FE*: *FI* was used to compare the increase in end-tidal concentrations of the two agents. Data were analysed using the Mann–Whitney *U* test. $P < 0.05$ was considered significant.

Ten patients received halothane, 12 received isoflurane. Numbers of males and females were equal in each group. Mean age (SD) in the halothane group was 64.9 (4.2) yr, in the isoflurane group 68.7 (7.1) yr. Hypotension after introduction of the volatile agent was similar in both groups.

The ratio *FE*:*FI* was significantly greater in patients receiving isoflurane at all times during the study (table I), showing that equilibration with the inspired concentration occurs more rapidly with isoflurane. This is consistent with previous studies on younger subjects and the lower blood-gas solubility of isoflurane.

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WHOLE BODY PROTEIN TURNOVER DURING ANAESTHESIA AND SURGERY

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Recent advances in the use and application of stable isotope technology have increased our knowledge of whole body protein turnover in man [1]. Previous workers have shown a depression of whole body protein synthesis and breakdown during anaesthesia, and have speculated that anaesthesia may be catabolic in surgical patients [2]. The purpose of this investigation was to re-examine whole body protein turnover in healthy subjects undergoing general anaesthesia as part of a well defined surgical model. Six healthy unpremedicated females were studied, mean age 44 yr (range 38–50 yr) and weight 65 kg (range 50–75 kg) scheduled to undergo elective total abdominal hysterectomy.

Anaesthesia consisted of thiopentone, pancuronium and enflurane. The lungs were ventilated to normocapnia with oxygen-enriched air. Normal saline was infused at a rate of 6 ml kg^{-1} h^{-1}. After a 12-h overnight fast, whole body protein turnover studies were started at 08.00 h using a primed-constant infusion of L-1 (^{13}C) leucine [3]. An isotopic steady state in plasma ^{13}C-ketoisocaproate (KIC) and expired ^{13}C-carbon dioxide were obtained before anaesthesia (2–4 h into the infusion), during anaesthesia (1 h), during surgery (1 h) and recovery (2 h). Collections of plasma and expired air were made during the steady state periods and plasma ^{13}C-KIC and ^{13}C-carbon dioxide enrichment measured to indicate precursor pool enrichment from which leucine flux and oxidation were calculated. Protein synthesis and breakdown rates were derived from these primary measurements. Mean whole body protein breakdown did not change with anaesthesia, but it decreased with surgery and during the first 2 h after surgery ($P < 0.05$). Mean protein synthesis did not change with either anaesthesia or surgery, but there was a significant decrease during recovery, from 77 (7.4) to 68.9 (7.6) μmol kg^{-1} h^{-1} ($P < 0.05$).

In conclusion, we were unable to demonstrate a change in whole body protein turnover during anaesthesia. The changes that were observed during surgery and during the first 2 h after operation were not of clinical significance.

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FACTORS EFFECTING HEADACHE FOLLOWING ANAESTHESIA FOR UROLOGICAL DAYCASE SURGERY

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Bell and colleagues [1] demonstrated a reduced incidence of headache following day-case gynaecological surgery if unpremedicated patients received a light breakfast 2 h before surgery. No similar reduction occurred after 5% dextrose i.v. It is suggested, therefore, that the "normality" of being allowed breakfast decreases stress-induced headache. This study investigated factors associated with postoperative headache following day-case urological surgery and attempted to suppress the symptom by the use of mild oral sedation.

Local Ethics Committee approval was obtained for this study in which ASA I and II patients admitted for day-case urological surgery were randomly allocated to receive either no premedication or temazepam 10 mg by mouth. All patients on one particular day received the same preoperative treatment and anaesthesia was induced with methohexitone 1.5 mg/kg body weight and maintained with nitrous oxide, oxygen and halothane via a Mapleson A system. Patients

TABLE II. *Percentage of patients with postoperative headache*

				P
"Normal" headache occurrence:				
> 1/week 75 %; > 1/month 32 %;		< 1/month	29 %	< 0.01
Percentage with postop. headache				
Females	62 %	Males	26 %	< 0.01
Age < 60 yr		Age 60 yr +		0.08
ASA I	41 %	ASA II	37 %	0 87
Bowels open	34 %	Bowels not open	44 %	0.52
Pre-op. headache	67 %	No pre-op. headache	36 %	0.16
First op.	56 %	Not first op.	32 %	0.07
1st op. this hospital	47 %	Not first op. this hospital	31 %	0.20
Temazepam	45 %	No premed.	35 %	0.50
Halothane	46 %	Enflurane	25 %	0.14

who had received halothane within the previous 6 months received enflurane.

The incidence of postoperative headache was investigated by an independent observer who recorded the patient's age, weight, ASA status, premedication and bowel status that day. A record was made of any headache presenting in the anaesthetic room and of the frequency with which the patient normally suffered headaches. Statistical analyses were performed using Student's t tests, analyses of variances (ANOVA), and logistic regression analyses as appropriate.

Eighty patients were studied (50 male) of whom 32 (40%) had postoperative headaches. Details of the patients and results of the study are presented in table II.

Logistic regression analysis revealed significant factors (in order of strength) to be: sex, frequent headache occurrence, first operation. There was a strong usual headache/sex interaction. Fifty percent of patients in the temazepam group complained of feeling cold after operation, compared with 19 % of unpremedicated subjects ($P < 0.01$).

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EVALUATION OF A BUPIVACAINE–MORPHINE MIXTURE FOR CAUDAL ANALGESIA IN CHILDREN

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Caudal injections of bupivacaine have limited duration of analgesic effect even when adequate volumes and concentrations are used [1]. Caudal morphine 0.1 mg kg^{-1} lasts longer [2]. We set out to determine if a smaller dose of morphine (0.05 mg kg^{-1}) combined with bupivacaine would provide the advantages of both agents while minimizing the potential disadvantages.

Following Ethics Committee approval and parental informed consent, we studied 30 healthy, unpremedicated patients, aged 11 months to 9 yr, undergoing orchidopexy, hernia or major penile surgery. They received standardized general anaesthesia and, before surgery, a 0.75-ml kg^{-1} caudal injection of either 0.125 % bupivacaine or 0.125 % bupivacaine with morphine 0.05 mg kg^{-1} by random allocation. Trained observers, unaware of the treatment, assessed postoperative pain for 24 h, using a score of 0–2 for each of five criteria (crying, movement, agitation, posture and localization of pain) to give a summed score of between 0 and 10. A total less than 4 was taken as adequate analgesia. In addition, they gave supplementary analgesia (paracetamol or i.m. nalbuphine) as they felt necessary. Ventilation rate and oxygen saturation were recorded using impedance pneumography and pulse oximetry. Chi-square analysis with Yates' correction was applied to nominal data and the Mann–Whitney U test for non-parametric data.

The two groups were comparable for age, weight and the nature and duration of surgery. There were significant differences for the first 6 h in the numbers of patients with adequate analgesia in the absence of nalbuphine: 13 or 15 in the combined bupivacaine and morphine group, compared with six of 15 for the bupivacaine alone group. Two patients were given paracetamol during this period, both in the bupivacaine alone group. Postoperative requirements for paracetamol were similar for both groups over the 24 h, whereas the requirements for nalbuphine differed significantly (table III). There were no detectable differences in the time to awakening, incidence of nausea and vomiting, or time to micturition after surgery. No patient in this study suffered from apnoea or ventilatory depression and, in particular, there were no detectable differences between the groups in either ventilatory rate or oxygen saturation.

TABLE III. *Cumulative number of patients requiring nalbuphine after operation.* *P < 0.05; **P < 0.01

	Time (h)				
	1	4	6	12	24
Bupivacaine alone ($n = 15$)	5 *	7 **	8 **	8 *	8 *
Bupivacaine–morphine ($n = 15$)	0	0	0	1	1

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EFFECTS OF FENTANYL AND ALFENTANIL ON THE CHANGE IN INTRAOCULAR PRESSURE PRODUCED BY SUXAMETHONIUM AND TRACHEAL INTUBATION

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Suxamethonium and tracheal intubation cause an increase in intraocular pressure (IOP) [1]. Fentanyl and alfentanil decrease IOP substantially [2]. This study assessed their effect on IOP during administration of suxamethonium and tracheal intubation.

Following Ethics Committee approval, 40 ASA I and II patients undergoing ophthalmic surgery were investigated. All received diazepam premedication. Before induction, control IOP, arterial pressure and heart rate were measured. Each patient then received 0.1 ml kg^{-1} of the study drug (fentanyl 2.5 μg ($n = 20$) or alfentanil 10 μg ($n = 20$)). After 3 min, anaesthesia was induced with thiopentone and suxamethonium 1.5 mg kg^{-1} and the vocal cords were sprayed with lignocaine before intubation. Ventilation was assisted to maintain E'_{CO_2} at 5% with 67% nitrous oxide and oxygen using a Bain type breathing system. All three measurements were repeated before administration of thiopentone and suxamethonium, and at 1, 2.5, 5, 7.5 and 10 min after the latter drug. After the study period anaesthesia was conducted according to our routine procedure.

There were no significant differences between the groups with reference to age, sex, weight or control values of all three measurements. ANOVA showed significant decreases in mean IOP, arterial pressure and heart rate in both treatment groups ($P < 0.001$) (table IV). Unpaired t test showed no significant differences between groups in the mean IOP changes from control values. Suxamethonium and intubation increased IOP in both groups. However, mean IOP values 1 min after suxamethonium were significantly lower than control in both groups. Post-intubation IOP was not significantly different from control values. It was significantly higher than pre-intubation values only in the fentanyl group. Although tracheal intubation produced significant increases in mean arterial pressure and heart rate, the increase was relatively small and lasted for only 1.5 min in both groups. No significant differences were noted between groups.

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TABLE IV. *Control value and reductions in IOP from control value (mean) (mm Hg). *Significantly less than control* (P < *0.001)*

	Control	Before induction	Before sux.	After sux.	After intub.	Overall decrease
Fentanyl	12	2.1	5.2	2.9*	0.3	5*
Alfentanil	11.9	2.1	6	2.7*	1.1	4.8*

HAEMODYNAMIC AND OXYGEN SATURATION CHANGES DURING UPPER GASTROINTESTINAL ENDOSCOPY: EVALUATION OF PROPOFOL AND MIDAZOLAM SEDATION

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Ideal characteristics of a sedative agent to facilitate elective outpatient endoscopy include a predictable dose–response curve, a short elimination half-life, rapid return to street fitness and cardiovascular and respiratory stability. Propofol possesses some of the ideal characteristics listed above [1]. The limited published data on cardiorespiratory effects of agents used for sedation suggest that alterations in the hypoxic drive to ventilation and respiratory mechanics may be associated with their use [2]. The objectives of this study were to assess the haemodynamic and oxygen saturation changes associated with propofol and midazolam sedation during elective upper gastrointestinal endoscopy.

Following institutional Ethics Committee approval and informed consent, 40 patients (ASA I–II) scheduled to undergo elective upper gastrointestinal endoscopy were randomly allocated to two groups. Group 1 ($n = 19$) received midazolam 81 (SD 32) μg kg^{-1}. Group 2 ($n = 21$) received propofol 0.95 (0.4) mg kg^{-1}. Drug administration was discontinued when patients demonstrated objective signs of sedation such as ptosis, slurred speech or nystagmus. Monitoring techniques included oxygen saturation (Critikon Oxy-shuttle), automatic pressure (Dinamap) and ECG (Hewlett-Packard). Haemodynamic and oxygen saturation data were recorded at the following times: 1 = baseline; 2 = i.v. access; 3 = topical anaesthesia of the oropharynx; 4 = injection of drug; 5 = insertion of mouth gag; 6 = insertion of endoscope; 7 = biopsy; 8 = removal of endoscope; 9 = min post-endoscopy.

All endoscopies were carried out by the same operator using an Olympus Q10 endoscope. Statistical analysis included analysis of variance (ANOVA), the Mann–Whitney U test and Fisher's exact probability test. $P < 0.05$ was considered significant.

The two patient groups were similar in age, weight, sex distribution and duration of the procedure. A reduction in oxygen saturation was observed at insertion of the endoscope (event 6) ($P < 0.02$). There were no significant differences in oxygen saturation between the two groups. An increase in heart rate was noted in both groups following endoscope insertion. However, the heart rate in propofol-treated patients (group 2) was significantly lower than in midazolam-treated patients (group 1) at insertion of the gag ($P < 0.05$) and removal of the endoscope ($P < 0.02$). Mean arterial pressure was reduced in both groups following drug administration, but a greater reduction was noted in group 2 patients ($P < 0.05$).

This study highlights the potential for the development of hypoxaemia and haemodynamic changes in patients undergoing elective upper gastrointestinal endoscopy following the administration of sedative doses of propofol and midazolam. The implications of this study for patient management are that vigilance and monitoring of patients are advisable if limited patient access is available and if the procedure is performed in darkened surroundings. Monitoring of arterial pressure, ECG and oxygen saturation should be routine.

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EFFECTS OF HALOTHANE ON ELECTRICALLY STIMULATED MOTOR EVOKED POTENTIAL IN THE EXTRADURAL SPACE

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Somatosensory evoked potentials recorded from the extradural space are known to be affected minimally by halothane anaesthesia [1]. Continuity of the anterior columns of the spinal cord can be assessed using motor evoked potentials. This study was designed to assess the effect of halothane on the motor evoked potential.

Informed consent of patients, parents, and the local Ethics Committee was obtained. We studied 16 adolescent patients with idiopathic scoliosis undergoing corrective surgery. Premedication was with papaveretum and hyoscine 60 min before the induction of anaesthesia. Before induction, two silver–silver chloride electrodes were attached to the scalp with collodium: the positive to the vertex and the negative over the leg area of the motor cortex. Anaesthesia was induced with propofol 2.5 mg kg^{-1} and intubation facilitated with pancuronium 0.08 mg kg^{-1}. The lungs were ventilated to normocapnia with a mixture of 70% nitrous oxide in oxygen. Once patients were positioned for surgery, the C7–T1 extradural space was identified and a bipolar recording electrode inserted. A Digitimer 180 stimulator was connected to the scalp electrodes and triggered by a Medelec MS 91 as described by Boyd [2]. A supramaximal response was recorded using the Medelec MS 91 recorder after 0, 15, 30, 40 and 50 min of anaesthesia. Patients were randomly assigned to two groups of eight patients. Group 1 received halothane maintained at an end-tidal concentration of 0.9%, while group 2 (control) received propofol administered via a three-stage infusion.

Peak-to-peak amplitude was similar in both groups and did not change in both groups in the study period. Median latency was 3.3 ms in the halothane and control groups at the beginning of the study period and did not change throughout anaesthesia.

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ESTIMATION OF CORE TEMPERATURE BY USE OF AN INSULATED ARM

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Insulation of a limb by reducing heat loss to a minimum allows the limb to warm rapidly towards core temperature as a result of continued heat supply from the body core. This enables the use of a limb site for monitoring core temperature.

Twenty ASA I patients receiving a standardized general anaesthetic for major gynaecological surgery were studied. Temperature probes were applied to the flexor aspect of each forearm 3 cm proximal to the wrist skin crease and 3 cm distal to the elbow skin crease, and secured with a single layer of tape (micropore). Core temperature was measured in the left aural canal as described by Holdcroft and Hall [1]. The right arm was wrapped in cotton wool bandage, whilst the left arm remained exposed. Temperature was recorded at each site every 5 min using an Edale 12-channel recorder. All i.v. drugs and fluids were given into the left arm at room temperature. Theatre temperature varied between 22.2 and 24.5 °C and the humidity was set at 60%.

After an initial increase, core temperature showed a steady decline of 0.01 °C min^{-1}. The temperature at the right (insulated) wrist increased towards core temperature and at 30 min the mean difference was 0.21 (SEM 0.07) °C. A logarithmic plot of the data showed a highly significant straight line fit for the insulated arm ($P < 0.001$ at both sites), indicating temperature change up to 25 min was a single component exponential, the time constant representative of which was 13.8 min. The slopes of the lines representing the insulated limb were notably steeper than those representing the exposed limb, demonstrating that temperature changed more rapidly in the insulated arm.

The use of an insulated arm for measurement of core temperature avoids many of the problems associated with the more conventional sites, and appears sufficiently accurate for use during routine surgery in situations where peripheral perfusion is not significantly impaired.

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TABLE V. *Changes in systolic function (%SS) and post-systolic shortening (%PSS) (mean (SEM)) with nitrous oxide or nitrogen under conditions of normal blood flow or critical constriction.* n = 7. *$P < 0.05$ *compared with nitrogen*

	Normal blood flow		Critical constriction	
	N_2	N_2O	N_2	N_2O
%SS	27.5 (6.2)	25.9 (5.4)	27.3 (6.9)	19 (6.4)*
%PSS	1.7 (3.2)	2.6 (4.6)	2.2 (4.5)	20.3 (17.5)*

EFFECT OF NITROUS OXIDE DURING BASAL PROPOFOL ANAESTHESIA ON MYOCARDIUM WITH NORMAL AND CRITICALLY RESTRICTED BLOOD SUPPLY

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In man, induction of anaesthesia with propofol causes cardiovascular depression that is enhanced in patients with coronary artery disease [1]. Nitrous oxide has been shown previously to induce regional dysfunction in the myocardium with limited blood supply [2]. The present study was designed to examine the influence on global and regional myocardial function of the addition of nitrous oxide to propofol by infusion under conditions of normal or critically restricted coronary blood supply.

Seven morphine-premedicated dogs (15–20 kg) underwent lateral thoracotomy under halothane anaesthesia. Cannulae were inserted to record aortic and left ventricular pressures; aortic and left anterior descending coronary artery (LAD) blood flows were measured by electromagnetic flowmeters. Piezo-electric crystals were implanted subendocardially in the regions supplied by the LAD and left circumflex coronary artery (LC) to measure segmental shortening. A micrometer controlled snare was placed around the distal LAD. Halothane was then replaced by propofol (5 mg kg^{-1} bolus, 0.3 $\text{mg kg}^{-1}\,\text{min}^{-1}$ maintenance). Data were collected after 60 min and again 10 min after 67% nitrous oxide replaced 67% nitrogen. On return to nitrogen, further data were collected. The snare was then tightened to obtain LAD critical constriction. After 20 min stabilization, further measurements were made in the presence of either nitrogen or nitrous oxide. Data were analysed using two-way ANOVA with Duncan's test or Wilcoxon matched paired tests as appropriate. $P < 0.05$ was considered significant.

During normal coronary blood flow, nitrous oxide caused reversible reduction in LV$dP/dt$ (−13%). During critical constriction, nitrous oxide caused reduction in LV$dP/dt$ and cardiac output by 20% and 9%, followed by incomplete recovery. Systolic function (%SS) decreased significantly and early diastolic dysfunction developed (post-systolic shortening (%PSS)) in the myocardium with critical constriction (table V).

Addition of nitrous oxide to basal propofol anaesthesia caused mild global haemodynamic depression. Systolic function decreased and early diastolic dysfunction increased significantly only in the presence of critical constriction.

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CARDIOVASCULAR AND RESPIRATORY EFFECTS OF KETOROLAC AND ALFENTANIL DURING ANAESTHESIA

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Opioids are used often to provide analgesia during operation, but depression of ventilation is undesirable in patients breathing spontaneously. Ketorolac tromethamine is a non-opioid analgesic which can be administered i.v. A previous study [1] demonstrated the morphine sparing effect of ketorolac in postoperative patients. The present study evaluated the intraoperative administration of ketorolac, compared with alfentanil.

Twenty patients (age 29–75 yr, weight 45–90 kg) were allocated randomly to receive either ketorolac 30 mg or alfentanil 0.5 mg. There were no significant differences between the groups for age, weight or sex. Informed consent was obtained. Two hours before operation, patients received temazepam 20–40 mg. Anaesthesia was induced with a sleep dose of propofol and suxamethonium was used to facilitate tracheal intubation. Anaesthesia was maintained with infusions of propofol and alfentanil, together with 60% nitrous oxide in oxygen. When the rate of ventilation was stable (±1 b.p.m. for 5 min), the alfentanil infusion was stopped, and the trial drug administered i.v. Mean arterial pressure (MAP), heart rate (HR) and rate of ventilation were measured. These data were stored to floppy disc during the 5-min period before administration of the test dose, and for 15 min thereafter.

There were no significant differences in the rates of infusion of propofol or alfentanil between the groups. There was no significant change in MAP, HR or rate of ventilation in the patients who received ketorolac, whereas MAP decreased from 86 to 72 mm Hg ($P < 0.01$) and HR from 66 to 59 beat min^{-1} ($P < 0.05$) in the alfentanil group. There was a significant reduction in the mean rate of ventilation in the alfentanil group, from 17 to 2 b.p.m. No patient developed apnoea in the ketorolac group, but in the alfentanil group, nine out of 10 became apnoeic ($P < 0.01$) for a mean period of 5.2 min. There was no significant difference between the groups in time to requirement for postoperative analgesia.

TABLE VI. *Onset and recovery of block with suxamethonium 250 or 500 μg kg^{-1} and halothane and fentanyl anaesthesia (mean (SEM)).* *P < 0.05; n = 10 *for all groups except where shown*

	Halothane		Fentanyl	
	MMG	IEMG	MMG	IEMG
Suxamethonium 500 μg kg^{-1}				
Max. block (%)	100(0)*	95.3(1.7)	100(0)*	95.7(0.5)
Time to max. block (min)	58.2(4.7)*	76.6(2.7)	62.6(8.3)	77.6(5.4)
Time (min) to				
T1 25%	5.4(0.6)*	4.8(0.6)	6.0(0.5)*	4.8(0.3)
T1 75%	6.5(0.6)	5.9(0.8)	8.1(0.6)*	7.0(0.5)
T1 100%	8.0(0.7)*	5.3(1.3) (*n* = 4)	9.1(0.6)	8.4(0.8) (*n* = 8)
Suxamethonium 250 μg kg^{-1}				
Max. block (%)	91.4(5.1)	85.1(3.6)	97.2(1.0)*	89.6(3.6)
Time to max. block (min)	72.1(3.0)	75.0(3.0)	75.9(4.3)	73.6(4.3)
Time (min) to				
T1 25%	3.3(0.6)*	3.1(0.5)	4.1(0.7)	4.0(0.7)
T1 75%	4.2(0.6)	3.9(0.5)	5.8(0.8)	5.2(0.8)
T1 100%	5.1(0.6)*	4.3(0.6) (*n* = 7)	6.8(0.5)	6.9(2.3) (*n* = 4)

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COMPARISON OF MECHANOMYOGRAPHY AND INTEGRATED ELECTROMYOGRAPHY FOR MONITORING SUXAMETHONIUM BLOCK

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Neuromuscular block is usually monitored by recording the twitch height of adductor pollicis muscle (mechanomyography (MMG)). The Datex Relaxograph which records integrated electromyography (IEMG) has been introduced as a simple monitor of neuromuscular block [1]. In the present study we have compared suxamethonium-induced neuromuscular block using these two methods of measurement.

Forty ASA I or II patients aged 16–65 yr were recruited to the study after giving their informed consent and with Ethics Committee approval. Following diazepam premedication and thiopentone 5–6 mg kg^{-1} induction, patients were randomly allocated to receive 0.45% halothane (end-tidal) in 70% nitrous oxide or fentanyl 4–5 μg kg^{-1} plus 50–100 μg increments as required. The IEMG responses of the hypothenar muscles of one hand were recorded by the Relaxograph while the mechanical responses of the adductor pollicis of the other were monitored by the Myograph 2000; both monitors operated in train-of-four (TOF) mode at 2 Hz every 10 s. Ten patients in each group were randomly allocated to receive either 250 or 500 μg kg^{-1} of suxamethonium. Maximum depression of the first twitch (T1) in the TOF sequence was recorded, as were the times from administration of suxamethonium to onset of maximum block and to recovery of T1 to 25, 75 and 100% of control.

The results are given in table VI. MMG showed greater depression of T1 in all groups, which was significant except in the halothane group receiving suxamethonium 250 μg kg^{-1}. The differences in the time to onset of maximum block were shorter with MMG monitoring, with only the higher dose of suxamethonium; this was significant for the halothane group. The times to recovery of T1 were generally longer with MMG. Whereas recovery is demonstrated with a good degree of consistency using MMG, 17 patients failed to show 100% recovery with IEMG, and two of those patients showed less than 75% recovery.

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PHARMACOKINETICS AND DISPOSITION OF ORG 9616 AND ORG 9426 IN THE CAT

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The search continues for non-depolarizing neuromuscular blocking agents with a fast onset, short duration of action and rapid recovery from neuromuscular blockade. Recent studies in animals have shown two new steroidal compounds, Org 9616 and Org 9426, possess most of these features. The time course of action of Org 9616 resembles, in various animal species, that of suxamethonium, while Org 9426 appeared to have a faster onset but duration of action similar to vecuronium in animals. However, unlike vecuronium, Org 9426 is stable in aqueous solution. The dispositions of these two compounds have been studied in cats with and without

TABLE VII. *Kinetic variables for Org 9616 and Org 9426 in cats with normal renal function (N) and ligated renal pedicles (R)*

Drug	$T_{\frac{1}{2}}\beta$ (min)	*Cl* (ml kg min)	$V\text{d}^{ss}$ (litre kg^{-1})	V_1 (litre kg^{-1})
9616 (N)	27 (14)	28 (11)	0.35 (0.33)	0.15 (0.15)
9616 (R)	50 (24)	23 (4)	0.47 (0.31)	0.13 (0.07)
9426 (N)	33 (6)	32 (11)	0.58 (0.24)	0.18 (0.06)
9426 (R)	34 (4)	20 (8)	0.42 (0.22)	0.12 (0.06)

ligated renal pedicles. Twenty-eight cats were anaesthetized with pentobarbitone. The carotid artery and common bile duct were cannulated to obtain blood and bile samples, respectively. In one group of animals the urethra was cannulated to collect urine samples, while in another group the renal pedicles were ligated in order to study the kinetics of the above compounds in the absence of renal elimination.

After injection of an iv. bolus dose of six times ED_{80} of either Org 9616 or Org 9426, blood, bile and urine (if applicable) were collected over a period of 8 h. At the end of each experiment, the liver was removed and the amount of drug stored within the organ determined. A gas-chromatographic assay was used to measure the concentration of Org 9616, its 3-desacetyl metabolite and Org 9426 in blood, bile, urine and liver homogenate. Plasma decay curves were fitted to a two-compartment model; the calculated kinetic parameters are shown in table VII.

Org 9616 and Org 9426 were excreted mainly into the bile. The renal elimination of both compounds was of minor importance, as reflected by the lack of changes in both time course of action and kinetic variables in animals with ligated renal pedicles. Org 9426 was mainly excreted as the parent compound; approximately 30% of Org 9616 was metabolized to its 3-desacetyl analogue. The total recovery from urine, bile and liver was 65% and 56% for Org 9616, and 86% and 85% for Org 9426, in animals with and without renal pedicle ligation, respectively.

Both the neuromuscular blocking profiles and kinetic characteristics of the two compounds appear to justify their further clinical development.

COMPARISON OF THE ELWELL NEUROMUSCULAR INDICATOR AND THE DATEX RELAXOGRAPH

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Train-of-four evaluation by tactile and visual means is not an accurate method of assessing residual neuromuscular block. Accurate methods are time consuming and expensive. We have developed a simple indicator of train-of-four recovery, that is semi-quantitative.

A National LM 3914 Bargraph Display Driver Integrated Circuit is used to drive a row of 10 light-emitting diodes. A piezo-ceramic transducer, normally used as a sounder in computers, is used as an accelerometer. The change in resistance is converted to a change in voltage. This voltage change gives a linear output via the integrated circuit and is displayed via the 10 LED.

Fourteen patients (seven male) aged 26–67 yr, ASA Class I or II, gave informed consent. Anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and fentanyl 1–2 µg kg^{-1} and maintained with 66% nitrous oxide and 1% isoflurane in oxygen. Atracurium 0.5 mg kg^{-1} was used to obtain neuromuscular block in all patients.

After induction of anaesthesia, and before neuromuscular blockade control values were obtained for both the Relaxograph and the Elwell Indicator, on the same arm.

The Elwell Indicator has 10 LED and control T1 and T4 was accepted as the minimum setting required to light 9 or 10 LED by each of the four twitch responses to train-of-four stimuli. The Relaxograph gave both a digital display and a print-out, while T1 and T4 had to be judged visually by observing the number of LED lit when using the Elwell Indicator.

Spontaneous recovery from neuromuscular blockade was compared using both devices. The comparison of T1 twitch height using both machines gave a correlation coefficient of 0.91, while comparison of T4 ratios gave a correlation coefficient of 0.94.

The Elwell Neuromuscular Indicator offers a cheap simple semi-quantitative method of assessing T4 ratio during recovery from neuromuscular blockade.

MATERNAL AND NEONATAL BUPIVACAINE CONCENTRATIONS AFTER SPINAL AND EXTRADURAL ANAESTHESIA FOR CAESAREAN SECTION

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There are few comparative studies of maternal and neonatal blood concentrations of bupivacaine after spinal and extradural anaesthesia [1].

In this study 41 healthy parturients with uncomplicated pregnancies, scheduled to undergo elective Caesarean section under regional anaesthesia, were randomly assigned to receive either spinal or extradural anaesthesia. Those in the spinal group received a bolus dose of 0.5% isobaric bupivacaine, and those in the extradural group received incremental doses of plain 0.5% bupivacaine. At the time of delivery, blood samples were collected from a maternal vein and the umbilical vein. Bupivacaine concentrations were measured using high pressure liquid chromatography, with a lower limit of reliable measurement at 50 ng ml^{-1} (CV$\pm$5%) Statistical evaluation was performed using Mann–Whitney U test or Chi-squared test (with Yates' correction).

The two groups were comparable with regard to maternal and gestational age. Maternal weights were comparable: spinal group 73.8 (2.0) kg (mean (SEM)); extradural group 69.3 (1.9) kg. Mean dose (range) of bupivacaine for each group was: spinal 0.14 (0.12–019) mg kg^{-1}; extradural 1.7 (1.2–3.0) mg kg^{-1} ($P < 0.001$).

Maternal bupivacaine concentrations were higher in the extradural group ($P < 0.001$) and all the neonates in that group had concentrations of bupivacaine greater than 50 ng ml^{-1}. Only one neonate from the spinal group had measurable concentration (85 ng ml^{-1}). This difference in distribution of sample values above and below the threshold of accurate measurement was highly significant ($P < 0.001$).

Despite these differences in bupivacaine concentrations, the neonates from the two groups had comparable neurobehavioural responses at 2 and 24 h [2].

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Dr Holt of the Guys Hospital Poisons Unit carried out the bupivacaine assay.

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ALKALINIZATION OF BUPIVACAINE FOR SCIATIC NERVE BLOCKADE

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The pH adjustment of bupivacaine has been reported to improve the quality and duration of extradural analgesia [1] and brachial plexus blockade [2] when compared with the commercial preparation. The purpose of this double-blind study was to assess if alkalinization of bupivacaine produced any effect on latency, duration of action or systemic absorption when used for sciatic nerve blockade.

Informed consent was obtained from 24 patients presenting for elective foot surgery and they were randomly allocated to received sciatic nerve blockade with either (group A) 0.5% bupivacaine with adrenaline 1:200000 (pH 3.9) in a dose of 2 mg/kg body weight or (group B) 0.5% bupivacaine with adrenaline 1:200000 with sodium bicarbonate 0.1 mmol litre^{-1} (0.1 ml) per 10 ml of solution (pH 6.4) in a dose of 2 mg/kg body weight. Sciatic nerve blockade was carried out by the posterior approach using a Stimuplex peripheral nerve stimulator. The temperature of each foot was continuously measured while analgesia to pinprick, touch sensation and motor power were assessed at 2-min intervals. Plasma concentrations of bupivacaine were measured regularly by high performance liquid chromatography (HPLC). Duration of useful analgesia was taken as the time to first postoperative analgesic requirement. Comparisons were made using the Mann–Whitney U test.

There were no differences in age, weight or nature of surgery between the two groups. There was a significant reduction in latency of nerve blockade (table VIII) with the alkanized solution. In addition, the duration of useful postoperative analgesia was prolonged from 14.1 h in group A to 18.3 h in group B. Plasma bupivacaine concentrations measured between 5 min and 90 min were not significantly different between the two groups. These results suggest that latency and duration of action of bupivacaine can be favourably altered by alkalinization when used for sciatic nerve blockade, without increasing systemic absorption.

TABLE VIII. *Mean (range) time (min) to onset of block*

	Group A	Group B	P
Temp. change	16.5 (10–24)	7.5 (2–15)	< 0.001
Analgesia	25.0 (14–38)	12.5 (4–20)	< 0.001
Touch	33.5 (22–45)	22.5 (12–36)	< 0.05

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EFFECTS OF BUPIVACAINE ON INWARD CURRENTS AND CONTRACTION IN SINGLE MYOCYTES ISOLATED FROM GUINEAPIG VENTRICLE

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Bupivacaine has been found to depress regional myocardial function *in vivo* [1]. The actions of bupivacaine were investigated in 51 single cells isolated from 10 guineapig hearts by enzymatic dispersion. The cells were superfused in an oxygenated balanced salt solution (36 °C, pH 7.4) containing calcium chloride 2.5 mmol litre^{-1}. Myocytes were voltage-clamped using a single microelectrode system [2]. The membrane potential was held at -40 mV and step depolarizations to 0 mV were applied. Current carried by calcium was measured as the peak inward current during a 200-ms depolarization. The calcium-activated current was recorded as a slow "tail" of inward current on repolarization following a 20-ms depolarization. Contraction was measured by an optical method [2]. In most experiments the stimulation frequency was 0.3 Hz. Student's t test was applied to the data.

Contraction was markedly reduced by bupivacaine 10 µmol litre^{-1}, while actions on membrane currents were small. At higher concentrations calcium current, calcium-activated tail current and contraction were depressed in a dose-dependent fashion (table IX).

In seven cells stimulated at 3 Hz, exposure to bupivacaine 10 µmol litre^{-1} depressed the calcium current by 18 (5)% ($P < 0.05$), calcium-activated tail current by 21 (4)% ($P < 0.05$) and contraction by 55 (5)% ($P < 0.01$). Inhibition of membrane currents and contraction was greater at 3 Hz than that observed in the same cells at 0.3 Hz ($P < 0.05$).

The magnitude of the calcium current is thought to reflect

TABLE IX. *Depression induced by bupivacaine* (%). n = *Number of cells.* *P < *0.05;* **P < *0.005*

	Bupivacaine concn (μmol litre^{-1})		
	10	33	100
n	26	6	12
Calcium current	2 (1)*	17 (2)**	27 (2)**
Tail current	5 (3)	21 (4)*	39 (4)**
Contraction	29 (1)**	43 (3)*	63 (3)**

calcium entry, whereas the tail current may indicate the cytosolic calcium transient [2]. The observation that bupivacaine 10 μmol litre^{-1} caused a marked reduction of contraction, with only small effects on these currents might be interpreted in terms of a depressant action on the myofilaments. Attenuation of calcium current and tail currents, seen at higher frequencies and concentrations, is consistent with the suggestion that reduced calcium entry and calcium release from the sarcoplasmic reticulum contribute to the depression of contractions under these conditions.

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SIGNIFICANCE OF PRELOAD ON MECHANOMYOGRAPHIC RELAXOMETRY IN INFANTS, CHILDREN AND ADULTS

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One method of quantification of the effect of neuromuscular blocking drugs is to measure the isometric contractile force of the adductor pollicis muscle after supramaximal stimulation of the ulnar nerve. To maintain isometric test conditions, Epstein and Epstein [1] recommended a muscular preload of 300–400 g in adults. The objective of this study was to compare data in infants and children.

Our measuring device consisted of a Statham-Gould UC 2 transducer protected from overload and rendered insensitive to traction by use of a UL 4-50 adaptor, a Neurostim T_4 nerve stimulator (HSE) and an amplifier with digital display of the preload with an accuracy of 1 g. The amplifier was triggered by the nerve stimulator; hence, mechanical interference effects on the transducer, which had no direct temporal correlation with a stimulus current impulse, could not disturb the recordings. By means of this device, the contractile force of the right adductor pollicis muscle after supramaximal ulnar nerve stimulation (single twitch 1 Hz *v.* train-of-four 2 Hz every 15 s) was measured in 10 infants (2–11 months), 10 children (2–4 yr) and 10 adults, with varying preloads ranging from 5 g to (adults) a maximum of 600 g.

On average the stimulus response in adults reached a maximum from a preload of 200 g onward and remained constant on further increase. In infants and children the maximum contractile force was measured at a preload of 15 and 75 g, respectively. Further increase in preload resulted in a marked reduction of contractile force in these age groups.

These results demonstrate that, compared with adults, in infants and children the optimum preload value is considerably lower and the optimum preload range is much smaller. Slight alterations during measurement may have a considerable impact on the level of contractile force in these age groups and may render impossible reference to the control value set at 100%. For this reason, caution must be exercised when interpreting results from studies in children in which the effects of neuromuscular blocking drugs have been measured mechanomyographically without use of the preload indicated here.

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ANTAGONISM OF VECURONIUM WITH NEOSTIGMINE IN CHILDREN: INFLUENCE OF THE ASSOCIATED HALOGENATED AGENT

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It was previously demonstrated that, following administration of neostigmine, the rate of recovery of vecuronium-induced neuromuscular blockade was slightly slower with isoflurane than with halothane in adults [1]. Halogenated agents are used widely in paediatrics, therefore we compared the rate of recovery in children to determine if it was affected by the halogenated agent used, as occurs in adults.

The procedure was approved by our Human Ethics Committee. Twenty children aged 3–10 yr undergoing minor elective surgery were studied. No child had any disease known to alter neuromuscular function. Anaesthesia was induced with nitrous oxide and halothane ($n = 10$) or isoflurane ($n = 10$). The ulnar nerve was stimulated at the wrist using train-of-four (TOF) with supramaximal square wave stimuli. The EMG response was monitored through surface electrodes placed over the adductor pollicis. When the EMG response was stable vecuronium 100 μg kg^{-1} was injected and the trachea intubated. Ventilation was controlled to maintain end-tidal $P\text{co}_2$ within normal limits (4–5%). Anaesthesia was maintained with nitrous oxide and an age-adjusted end-tidal concentration (1 MAC) of halothane or isoflurane. When the first twitch spontaneously reached 10% of the control twitch height (TH), neostigmine 30 μg kg^{-1} and atropine 10 μg kg^{-1} were administered. Both TH and TOF were observed every 1 min during a 15-min period. Recovery time from 10% to 90% of control was also measured. Mann–Whitney *U* test and Kruskall–Wallis test were used. $P < 0.05$ was considered to be significant.

Ten minutes after administration of neostigmine, TH reached 99 (1)% and 92 (10)% ($P < 0.01$) in the halothane and the isoflurane groups, respectively. A TOF ratio of 0.7 was obtained in less than 6 min during halothane anaesthesia, whereas it took 8–10 min in the isoflurane group. Beyond 6 min the TOF ratio was significantly higher in the halothane group. Recovery time was significantly slower in the isoflurane group (8.0 (3.8)) than in the halothane group (5.0 (1.8)) ($P < 0.05$).

In children, in contrast to Dernovoi's study [1] in adults, the rate of recovery of vecuronium-induced neuromuscular blockade seemed to be more influenced by the halogenated agent used. This could result from the more pronounced depressant effects of isoflurane on the neuromuscular junction. Rupp [2] noted that isoflurane increased the vecuronium neuromuscular blockade to a greater extent than did halothane.

In conclusion, following administration of neostigmine, a TOF ratio of 0.7 can be obtained in less than 10 min in children during halothane or isoflurane anaesthesia. Nevertheless, the rate of recovery from neuromuscular blockade is slower with isoflurane than halothane in children.

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DECAY IN BLOOD CHLOROFORM CONCENTRATIONS AFTER ANAESTHESIA

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Chloroform was administered to six patients undergoing routine urological surgery. Their ages ranged from 32 to 67 yr (mean 53.3). Consent for serial blood sampling during the postoperative period had been obtained.

Premedication consisted of temazepam 20 mg (three patients), promethazine and atropine (one patient), papaveretum and atropine (two patients).

Anaesthesia was induced with thiopentone 5.5–7.5 mg kg^{-1} i.v. and continued with spontaneous inhalation of up to 3.5% chloroform in oxygen, delivered by a Cyprane Chlorotec vaporizer via a Magill attachment and facemask or tracheal tube for between 12 and 53 min (mean 37.1 min).

A Teflon cannula inserted into a peripheral vein was used to draw heparinized blood samples for up to 12 h from the time of cessation of administration of chloroform.

Blood chloroform concentrations were determined by means of a Perkin Elmer gas chromatograph with Carbowax 400 (polythene glycol) as stationary phase. A flame ionization detector and digital integrator were used to produce and compare chloroform curves in the samples and in standard solutions. The concentration of each sample was measured twice, and a mean value obtained. Variation between measured values was less than 10%. The method measured blood chloroform concentrations greater than 0.12 mg dl^{-1} reproducibly, and comparison between standard and measured concentrations produced a near linear curve ($r = 0.996$, $c = 0.13$ mg dl^{-1}).

Blood concentrations at the cessation of administration of chloroform ranged from 9.0 to 17.4 mg dl^{-1} (mean 11.4) (fig. 2). Chloroform was undetectable by this method in any sample drawn after 10 h. All patients regained consciousness within 15 min of cessation of chloroform adminstration, during the period of rapid decrease in blood chloroform concentrations.

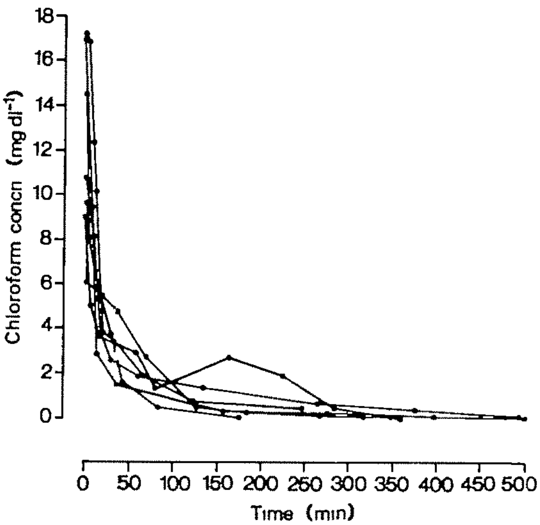

FIG. 2. Concentrations of chloroform in venous blood *v.* time after cessation of administration.

INFLUENCE OF ALCOHOL CONSUMPTION ON THE INDUCTION DOSE OF THIOPENTONE

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Animal studies suggest that regular alcohol consumption produces resistance to the anaesthetic, but not the cardiorespiratory, effects of anaesthetic drugs. However, there is disagreement as to whether this applies to man [1,2]. Swerdlow and Holly [3], using spectral edge analysis, recently concluded that alcohol intake does not influence the induction dose of thiopentone, but their studies were carried out on small numbers of patients. This study was carried out to assess the effect of alcohol consumption on the induction dose of thiopentone in a large group of patients.

Five hundred and thirty-two healthy unpremedicated patients were studied. On the basis of their admitted alcohol consumption, they were classified as "drinkers" or "non-drinkers". Non-drinkers included abstainers or occasional imbibers while drinkers took more than the equivalent of 2 pints of beer (alcohol 40 g) per week or who had drunk more than 6 pints (120 g) in the previous month.

Thiopentone 2.0 mg kg^{-1} was injected into a large forearm vein over 20 s followed by 25-mg increments every 15 s until the eyelash reflex was abolished or contact with the patient was lost. The total dose was noted. The average dose in each age decade was analysed using independent samples t test and multiple regression analysis.

Those patients regularly consuming alcohol required significantly large doses of thiopentone to induce anaesthesia

TABLE X. *Mean (SEM) induction dose of thiopentone (mg kg^{-1}) by age decade.* n = *Number of patients in group*

Age (yr)	Non-drinkers		Drinkers		
	Dose	*n*	Dose	*n*	
20–29	4.5 (0.16)	64	5.6 (0.27)	27	< 0.001
30–39	4.1 (0.16)	53	5.6 (0.25)	29	< 0.001
40–49	4.3 (0.16)	46	5.1 (0.30)	28	< 0.01
50–59	3.9 (0.14)	52	4.7 (0.21)	26	< 0.001
60–69	3.3 (0.10)	80	4.4 (0.23)	14	< 0.001
70–79	3.0 (0.09)	61	3.6 (0.22)	14	< 0.01
80–89	2.9 (0.12)	34	3.6 (0.32)	4	< 0.06

(table X). After adjustment for differences in age and weight distribution, men who were heavy users of alcohol (> 40 g daily) required 33% more thiopentone for induction than non-drinkers, while women required 44% more.

This study demonstrates increased barbiturate requirements in subjects who consume more than 40 g of alcohol weekly.

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COMPARISON OF THE EFFECTS OF SEDATION WITH MIDAZOLAM OR KETAMINE ON THE AIRWAY MUSCLES

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Although both midazolam and ketamine are used for sedation, for example in association with regional anaesthesia, they have different effects on ventilation, particularly on the patency of the upper airway. Undetected airway obstruction may be disastrous in these circumstances [1].

After Ethics Committee approval and informed consent, 23 male patients, ASA physical status I or II, were studied before operation. Patients with overt cardiovascular disease or hypertension, and those older than 75 yr or more than 120% of expected weight were excluded. Premedication was with temazepam 20 mg by mouth 1 h before the study started. Patients were randomly allocated to receive either midazolam or ketamine. Midazolam was administered i.v. until the eyelids drooped but did not close, attempting to preserve responses to either verbal contact or touching the face, and the eye-lash reflex. Ketamine was given at a fixed dose of 1 mg kg^{-1} i.v. Studies were done before sedation, after satisfactory sedation had been achieved, and before, during and after episodes of airway obstruction if these occurred.

Electrodes were attached below the chin (tongue), and over the sternohyoid (strap) and scalene muscles, and the EMG recorded on FM tape along with the ECG. Analysis was by replay through a delay unit to allow the ECG to be gated out, followed by rectification and integration (time constant 100 ms) to allow comparison of muscle activity. Activity was expressed as % of the values before sedation, and summarized as quartiles, as distribution was not normal. Comparisons within and between groups were with the appropriate Wilcoxon tests.

TABLE XI. *Muscle activity (% of awake values) (mean and quartiles)*

	Tongue	Strap	Scalene
Midazolam			
Clear airway	43	50	29
($n = 12$)	22–50	25–70	15–66
Obstructed	62	94	56
($n = 10$)	36–160	55–260	28–132
Ketamine ($n = 11$)	73	175	100
	48–167	157–283	65–350

The groups were comparable in terms of age, height and weight (% expected). The mean (SD) dose of midazolam used was 5.6 (1.4) mg. Midazolam caused the activity of the strap and scalene muscles to change from tonic to phasic. Marked increases in phasic activity occurred during episodes of obstruction which were relieved by extending the head. No airway obstruction was detected after ketamine. The results are summarized in table XI. All the differences between the groups, and between the clear and obstructed states, were significant ($P < 0.01$).

This study confirms the clinical observation that airway maintenance with ketamine is good and shows that the airway muscle tone is relatively well sustained.

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EFFECTS OF HALOTHANE, ISOFLURANE AND ENFLURANE ANAESTHESIA ON THE TOTAL VENTILATORY IMPEDANCE OF PONIES

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The effects of general anaesthesia on total ventilatory impedance were studied in a group of six healthy Shetland ponies. Before an experiment the animals were starved overnight, with free access to water. No premedication was given and anaesthesia was induced by inhalation of the appropriate agent (halothane, isoflurane or enflurane) from a large animal circle system using oxygen as the carrier gas. When the pony was unconscious it was placed in right lateral recumbency and a strip of rubber with a T-shaped cross-section passed through the larynx via the nares under endoscopic control. This prevented laryngeal closure, which would invalidate the impedance measurements.

The fresh gas flow rate and anaesthetic agent concentration were adjusted to maintain the animals in a light surgical plane of anaesthesia as judged by standard clinical parameters. The animals were connected to the circle system for the whole experiment except when impedance measurements were made.

Measurements of total ventilatory impedance were made every 10 min using the forced random noise method first described by Michaelson, Grassman and Peters [1] and modified for use in horses by Young and Hall [2].

Only small changes in total ventilatory impedance were seen during 30 min of halothane or 60 min of isoflurane anaesthesia. Enflurane, in contrast, had a dramatic effect on ventilatory mechanics. A marked, progressive increase in impedance and resistance was seen. The increase was frequency-dependent, with little change above 15 Hz. There was a large variability in the response of individual animals.

There is, as yet, no explanation for the increase in impedance with enflurane. The site of action could be upper airway, lower airway or both, although volatile anaesthetic agents usually cause a decrease in lower airway resistance.

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ESTIMATION OF Pa_{CO_2} FROM END-TIDAL PCO_2 AND Hb SATURATION IN CYANOTIC CHILDREN

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A previous study [1] demonstrated the theoretical and observed relationships (quasi-hyperbolic functions) between Pa_{O_2} and the alveolar deadspace fraction $V\mathrm{D}^{alv}/V\mathrm{T}^{alv}$ in a group of children with congenital heart disease, some of whom had right–left (RL) intracardiac shunts. It was found that well-oxygenated children had alveolar deadspaces close to the theoretical minimum, whereas carbon dioxide elimination in the cyanotic children was somewhat less efficient than predicted. There was also a strong linear relationship between Pa_{O_2} and the arterial to end-tidal carbon dioxide difference ($Pa_{CO_2} - P\mathrm{E}'_{CO_2}$), in children with Pa_{O_2} values of less than 10 kPa at an $F\mathrm{I}_{O_2}$ of 0.5; $(Pa_{CO_2} - P\mathrm{E}'_{CO_2})$ (kPa) $= 2.37 - 0.214 \times Pa_{O_2}$ (kPa); $n = 20$, residual standard deviation (RSD) $= 0.46$, $r = -0.61$, $P < 0.01$. Mean $(Pa_{CO_2} - P\mathrm{E}'_{CO_2})$ in children with good oxygenation was 0.00 (0.15) kPa.

The present study investigated the relationship between $(Pa_{CO_2} - P\mathrm{E}'_{CO_2})$ and arterial haemoglobin saturation (Sa_{O_2}) as measured by pulse oximetry. Should a strong relationship be demonstrable, it would be possible to estimate Pa_{CO_2} from $P\mathrm{E}'_{CO_2}$ and Sa_{O_2},—that is, non-invasively, in children with RL shunts.

Twenty observations were made in nine children undergoing open or closed heart surgery. Anaesthesia was provided with fentanyl and nitrous oxide (50% in oxygen) and ventilation was controlled by a Servo Ventilator 900C. Signals from the ventilator and from a 930 CO_2 Analyzer were led to a computer which produced, on-line, a carbon dioxide single breath test [2,3] from which $P\mathrm{E}'_{CO_2}$ was obtained. Pa_{CO_2} and Pa_{O_2} were obtained by sampling from an indwelling arterial catheter. Sa_{O_2} was obtained by pulse oximetry: Novametrix 500 ($n = 6$) or Radiometer Oxi ($n = 3$). The relationship between $(Pa_{CO_2} - P\mathrm{E}'_{CO_2})$ and Sa_{O_2} was:

$$(Pa_{CO_2} - P\mathrm{E}'_{CO_2}) = 4.93 - 0.0493 \times Sa_{O_2}$$

($r = -0.73$; $P < 0.001$; RSD $= 0.33$).

The relationship between $(Pa_{CO_2} - P\mathrm{E}'_{CO_2})$ and Pa_{O_2} was:

$$(Pa_{CO_2} - P\mathrm{E}'_{CO_2}) = 2.37 - 0.240 \times Pa_{O_2}$$

($r = -0.77$; $P < 0.0001$; RSD $= 0.31$).

The results of the present and previous studies suggest that knowledge of Sa_{O_2} should allow an approximate estimate of Pa_{CO_2} to be made from $P\mathrm{E}'_{CO_2}$ in cyanotic children. For instance, an Sa_{O_2} of 80% would be associated with an arterial to end-tidal PCO_2 difference of 0.5–1.5 kPa. At Sa_{O_2} 70%, the difference would be approximately 2 kPa.

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ARTERIAL OXYGENATION AFTER DIFFERENT TYPES OF MAJOR HEAD AND NECK SURGERY

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After non-thoracic surgery, hypoxaemia which persists beyond the immediate postoperative period is said to be more severe after upper abdominal surgery and to be the result of pain and spasm of the abdominal muscles reducing lung volume [1]. We have reported persistent hypoxaemia in 12 patients after head and neck surgery involving tracheotomy which showed no sign of recovery at 7 days. It was suggested that hypoxaemia was caused by a reduction in lung volume secondary to the effect of the tracheostomy in by-passing the upper airway [2]. In six of the patients, surgery was confined to the head and neck, but in six it extended to the superficial tissues of the chest wall. The lung volume (vital capacity) and arterial blood-gas data have been re-analysed to determine if there was any difference in the pattern of change after operation between the two types of surgery.

Mean (SEM) age of the six patients (all male) whose surgery involved only the head and neck was 61 (4) yr and of the group (5 male, 1 female) whose surgery involved the superficial tissues of the chest wall was 55 (4) yr. Vital capacity (VC) of the patients having surgery confined to the head and neck decreased to 65% of the preoperative value the first day after operation ($P < 0.01$). By day 7, VC was 72% of its preoperative value—not significantly different from day 1. Pa_{O_2} decreased from 11.3 (0.4) kPa before operation to 9.5 (0.8) kPa on day 1 ($P < 0.01$) and to 9.2 (0.3) kPa on day 7 (ns). VC of the patients whose operation involved the chest wall decreased to 57% of the preoperative value on day 1 ($P < 0.01$) and increased to 80% of the preoperative figure by day 7 ($P < 0.01$). Pa_{O_2} decreased from 12.6 (0.5) kPa before operation to 11.1 (0.6) kPa on day 1 ($P < 0.05$) and by day 7 had decreased further to 9.9 (0.4) kPa ($P = 0.05$). Pa_{CO_2} did not alter in both groups.

It is concluded that the pattern of change in lung volume and arterial oxygen saturation after major head and neck surgery is affected by extension of the surgery to the superficial tissues of the chest wall. The pattern of change in Pa_{O_2}

after head and neck surgery involving the chest wall appears to be unrelated to the pattern of change in lung volume.

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COMPARISON OF TOTAL VENTILATORY COMPLIANCE IN SEDATED AND ANAESTHETIZED INFANTS AND YOUNG CHILDREN

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Lung compliance is known to decrease on induction of anaesthesia in the adult, but few studies have been carried out in the infant.

The aim of this study was to compare total respiratory compliance (*C*rs) in the preoperative sedated infant and during halothane–nitrous oxide anaesthesia.

Following premedication with Triclofos sodium 50–100 mg kg^{-1}, infants undergoing elective surgery were studied using the multiple occlusion technique which has been validated in this Department [1]. This method of measuring compliance in infants has been described at a previous meeting of the Anaesthetic Research Society [2]. The infants were initially studied asleep on the ward. Measurements of compliance were repeated following induction of anaesthesia and intubation using suxamethonium, when spontaneous ventilation with regular tidal breathing had recommenced.

Seventeen patients, aged between 1 and 25 months, were successfully studied in both the sedated and the anaesthetized state. The decrease in *C*rs on induction of anaesthesia was highly significant ($P < 0.001$). The mean decrease was 34.8%, and the range 0–58%. Figure 3 shows the consistent individual decrease in *C*rs in all but one of the 17 patients.

The decrease in compliance on induction of anaesthesia probably reflects the decrease in lung volume that is known to occur, such that tidal breathing occurs along the lower, flattened portion of the pressure–volume curve of the lung.

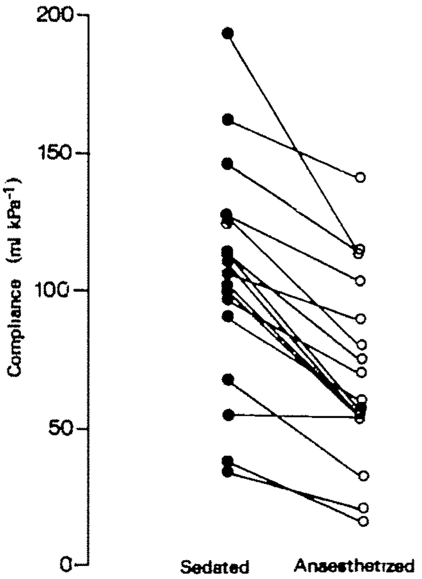

FIG. 3. Total ventilatory compliance in 17 infants during sedation and following induction of anaesthesia.

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EFFECT OF ORAL MIDAZOLAM AND DIAZEPAM ON SOME PULMONARY FUNCTION TESTS

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Midazolam and diazepam when injected i.v. depress the central ventilatory drive [1, 2]. This study investigated the effect of midazolam and diazepam on some pulmonary function tests. Sixteen female patients of average age 46.9 (SD 10.5) yr and weight 62.6 (SD 8) kg free of pulmonary disease and not receiving any drugs were studied. Vital capacity, forced vital capacity, maximum voluntary ventilation and peak expiratory flow were measured in each patient before and 30, 60, 90 and 120 min after oral administration of midazolam 15 mg. On the following day the same measurements were repeated in the same sequence after diazepam 15 mg by mouth. Two patients were excluded from the study after midazolam because they were too drowsy for further measurements.

The results (table XII) were analysed with two factors and repeated measures analysis of variance. We found a significant difference between the subjects for all the parameters measured. Variation of drug effect was significant for peak expiratory flow (PEF) (F actual = 5.21; F critical = 3.93). Comparisons of PEF values (Bonferroni corrected t tests) revealed a statistically significant difference only between the mean values before and 90 min after midazolam (t actual = 3.63; t critical = 2.86). No significant difference was found between the PEF values before and after diazepam or between the PEF values 90 min after adminstration of midazolam or diazepam. A significant interaction between subjects and drug influence was found for vital capacity, maximum voluntary ventilation and peak expiratory flow, where F critical = 1.81 *v.* F actual values 2.2, 2.3, 1.82, and 2.24, respectively.

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TABLE XII. *Mean (SEM) vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), maximum voluntary ventilation (MVV) and peak expiratory flow (PEF) before and 30, 60, 90 and 120 min after midazolam by mouth or diazepam by mouth*

	Before drug	Time after drug (min)			
		30	60	90	120
Midazolam					
VC (litre)	3.2 (0.2)	3.2 (0.2)	3.1 (0.2)	3.1 (0.2)	3.2 (0.2)
FVC (litre)	3.3 (0.3)	3.2 (0.1)	3.1 (0.2)	3.2 (0.2)	3.2 (0.2)
FEV_1 (litre)	2.5 (0.1)	2.5 (0.1)	2.5 (0.1)	2.4 (0.2)	2.5 (0.1)
MVV (litre min^{-1})	78 (4.2)	75 (3.7)	75 (4.3)	75 (4.5)	75 (4.4)
PEF (litre min^{-1})	5.8 (0.3)	5.5 (0.3)	5.3 (0.3)	5.0 (0.2)	5.3 (0.2)
Diazepam					
VC (litre	3.2 (0.2)	3.2 (0.2)	3.1 (0.2)	3.2 (0.2)	3.2 (0.2)
FVC (litre)	3.3 (0.2)	3.1 (0.2)	3.2 (0.2)	3.2 (0.2)	3.2 (0.2)
FEV_1 (litre)	2.4 (0.2)	2.4 (0.2)	2.4 (0.1)	2.5 (0.1)	2.4 (0.1)
MVV (litre min^{-1})	76 (4.2)	76 (4.2)	75 (4.4)	75 (4.3)	75 (4.4)
PEF (litre min^{-1})	5.8 (0.2)	5.7 (0.3)	5.6 (0.2)	5.5 (0.2)	5.4 (0.3)

GABA INVOLVEMENT IN SPINAL ANALGESIA WITH MIDAZOLAM

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Intrathecal injections of the water soluble benzodiazepine, midazolam (Hypnovel, Roche) have been shown in the rat to produce spinally-mediated analgesia by binding with spinal cord benzodiazepine receptors [1]. It is generally accepted that the hypnotic and anticonvulsant properties of benzodiazepines are mediated by a GABA receptor–benzodiazepine receptor–chloride channel complex [2]. The purpose of this study was to determine if the segmental analgesia following intrathecal injection of midazolam involved GABA. We used three different doses of the GABA antagonist bicuculline which were given intrathecally with equipotent doses of midazolam, ketocyclazocine or fentanyl (Sublimaze, Janssen).

Male Wistar rats with chronically-implanted lumbar subarachnoid catheters were allocated to three groups. Electrical current thresholds for pain (ECTP) were measured in the skin of the tail and neck as previously described [1]. Segmental analgesic responses were measured following 10-µl intrathecal injections of equieffective doses of each agonist alone and also after intrathecal injections of each agonist mixed with a range of doses of bicuculline. The effect of each dose of bicuculline was calculated as a percentage suppression of the control agonist response.

All three agonist drugs caused segmental analgesic blocks. The highest dose of bicuculline (5 pmol) had no effect on its own. Bicuculline caused a dose–dependent suppression of the analgesic responses to midazolam, but did not suppress the opioid responses (fig. 4).

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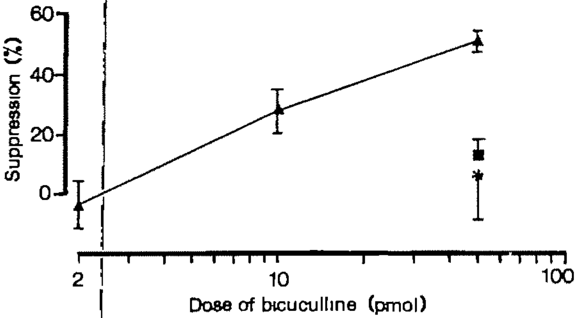

FIG. 4. Suppression of analgesic responses to midazolam (▲) by bicuculline (mean values and SEM). *Ketocyclazocine 40 nmol; ■ fentanyl 6.8 nmol.

NALOXONE ANTAGONIZES THE SPINAL ANALGESIC EFFECTS OF MIDAZOLAM

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We compared antagonism of spinal analgesic effects of intrathecal midazolam and two opioids (ketocyclazocine and fentanyl) by naloxone and flumazenil (drugs acting specifically on opioid and benzodiazepine receptors, respectively).

Male Wistar rats with chronically implanted lumbar subarachnoid catheters were used; electrical current threshold for pain (ECTP) was measured in the tail and neck, before and after intrathecal injection of 10 µl of an agonist. The response was standardized as the ratio of three ECTP readings after intrathecal injection of agonist and three control readings. Equieffective doses of each agonist were determined from dose–response studies performed in the absence of antagonists. The responses to these doses of each agonist were measured in the presence of a range of doses of intraperitoneal antagonist. The percentage inhibition of the anti-

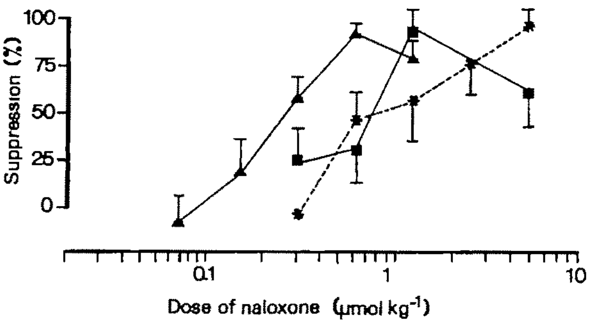

FIG. 5. Dose–dependent suppression (mean and SEM) of response to fentanyl (▲), ketocyclazocine (■) and midazolam (*) by naloxone.

nociceptive effect of each agonist was then plotted against dose of antagonist.

All animals demonstrated segmental analgesia. Both naloxone and flumazenil had no effect on ECTP when used alone. Naloxone produced a dose–dependent suppression of response to all three agonists (fig. 5). The naloxone dose–response curve for suppression of midazolam response lies to the right of the fentanyl curve and overlies that for ketocyclazocine. Flumazenil produced a dose–dependent suppression of the midazolam response and had no effect on fentanyl or ketocyclazocine.

The antinociceptive effects of midazolam and ketocyclazocine are antagonized by similar doses of naloxone. The absence of effect of flumazenil on the ketocyclazocine response suggests that the two drugs do not bind to a common receptor site. We conclude that midazolam spinal antinociception is mediated via the kappa opioid pathway.

X-RAY LARYNGOSCOPY IN PATIENTS WITH A HISTORY OF DIFFICULT LARYNGOSCOPY DURING PREGNANCY

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It has been suggested that failure to intubate the trachea of an obstetric patient may sometimes be attributable to anxiety or inexperience on the part of the anaesthetist [1]. The physical changes of pregnancy are also relevant. We have previously reported x-ray laryngoscopy findings in normal volunteers and in patients with a history of difficult laryngoscopy unrelated to pregnancy [2,3]. Following local Ethics Committee approval, the technique was extended to patients with a history of difficult laryngoscopy associated with the later stages of pregnancy. In a District General Hospital with a Maternity Unit dealing with approximately 4500 deliveries per annum, the Anaesthetic Events Records disclosed 12 cases of difficult intubation over a 4-year period (1983–1986 inclusive). The estimated incidence of this problem was 1 in 140 general anaesthetics.

Ten of these patients were traced and, after explanation, eight consented to this form of investigation. The details of the methodology were as described previously [2,3]. In three of these patients laryngoscopy demonstrated either the posterior commissure or the arytenoids, giving a clear indication of the position of the laryngeal inlet (Grade 2). In the remaining five subjects the epiglottis was seen, but no laryngeal structures beneath it (Grade 3).

Failure to control the hyoid with the laryngoscope blade tip, commented on in our previous x-ray laryngoscopy papers, was again the important feature in all the difficult cases. In all three Grade 2 laryngoscopies, the blade tip was closely related to the hyoid and the epiglottis was elevated. In four of the Grade 3 laryngoscopies the blade tip was not related to the hyoid and the epiglottis was not elevated. The remaining patient, also Grade 3, had a partly raised epiglottis with the blade tip nearer to the hyoid and below its body.

Our results suggest that approximately 50 % of the patients who present difficulty with intubation in pregnancy remain difficult in the non-pregnant state. Anaesthetist anxiety and inexperience may have been relevant in the remaining group, although none of these patients was less than Grade 2 at the time of assessment.

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BLOOD:CSF GLYCINE CONCENTRATION GRADIENT FOLLOWING A CONTROLLED I.V. INFUSION IN DOGS

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Glycine solution 1.5 % is the standard irrigation fluid for transurethral prostatectomy (TURP). Neurological complications such as pupillary dilatation, visual disturbances [1] and delayed emergence from anaesthesia [2] have been attributed to excessive systemic absorption of glycine or neurotransmitter effects of metabolites. Prolonged visual evoked responses have also been associated with increased plasma glycine concentrations in man [3]. The aims of this study were to measure the plasma and CSF pharmacokinetic profiles of glycine following a controlled i.v. infusion in dogs and to quantify its plasma CSF concentration gradient.

Following institutional research committee approval, six male greyhounds (weights 25–55 kg) were studied. Anaesthesia was induced with thiopentone 25 mg kg^{-1} and maintained with 60 % nitrous oxide and 1.5 % halothane in oxygen. Following tracheal intubation, controlled normocapnic ventilation was instituted. The femoral artery was cannulated for monitoring of arterial pressure and blood sampling. Continuous ECG, arterial pressure, end-tidal carbon dioxide and temperature were monitored. A 16-gauge Tuohy needle was located in the cisterna magna to facilitate CSF sampling. Glycine solution 1.5 % was infused i.v. at the rate of 5 mg kg^{-1} min^{-1} from 0 to 30 min. Simultaneous plasma and CSF samples were taken at 0, 10, 20, 30, 40, 50, 60, 90, 120 and 150 min. Glycine concentrations were assayed using an ion exchange chromatography technique. Three samples for serum sodium and osmolality were also taken at 0, 60 and 180 min. Repeated measures analysis of variance was applied to the results.

There was no significant change in serum sodium or osmolality through the study period.

In this study, designed to simulate near clinical conditions, a 10-fold increase in plasma and CSF glycine concentrations was observed following controlled i.v. infusion. Peak CSF glycine concentrations were noted 30 min after peak plasma concentrations and a 1:50 concentration gradient was observed. The delayed reduction in CSF glycine and its role as an inhibitory neurotransmitter may explain neurological disturbances and delayed emergence from general anaesthesia following TURP.

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HYPERVENTILATION HAEMOLYSIS: ARE HUMANS AT RISK?

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In 1963 Bindslev [1] demonstrated that destruction of red cells (haemolysis) occurred in the blood of dogs subjected to hyperventilation to a Pa_{CO_2} of approximately 1.5 kPa. By manipulation of blood pH, using acidotic and alkalotic infusions, he concluded that the haemolysis was primarily a function of the blood hydrogen ion concentration, and this became severe at values of pH in excess of 7.7. This finding has been confirmed by others.

This phenomenon of alkalaemic haemolysis has only recently become of clinical interest, with the introduction of extracorporeal carbon dioxide removal (ECCO$_2$R), in which high values of carbon dioxide extraction are achieved from a low flow veno–venous circulation to assist in the management of acute respiratory failure. For example, in one animal study of ECCO$_2$R, a carbon dioxide extraction of 17.8 ml (STP) dl^{-1} was associated with a pH of 7.67 in the blood returning to the subject from the membrane lung [2].

TABLE XIII. *Plasma haemoglobin concentration as a function of pH*

pH (mean (SD))	Plasma Hb (mg dl^{-1}) (mean (SEM))	*n*
7.23 (0.03)	55.6 (12.4)	9
7.37 (0.04)	69.9 (9.8)	9
7.50 (0.04)	60.9 (11.7)	8
7.69 (0.07)	81.2 (22.1)	7
7.93 (0.07)	55.9 (14.3)	6

This study was designed to examine if alkalaemic haemolysis occurs in human blood. Eleven healthy laboratory staff gave informed consent to donate 450 ml of blood via the Oxford Transfusion Service. Heparin solution 30 ml (2250 iu) provided anticoagulation. Thirty-nine experiments were performed, each involving the equilibration over 60 min of 80 ml of blood with a carbon dioxide concentration in air equal to one of 12 values in the range 0–5.5%. Equilibration was achieved using repeated circulation of blood at 60 ml min^{-1} through a laboratory-built polypropylene membrane lung with a priming volume of 60 ml. Blood samples were taken every 10 min and analysed for pH, using a precalibrated Radiometer ABL2 Laboratory, and for plasma haemoglobin (Hb) concentration, according to the method of Standefer and Vanderjagt [3].

Measurements of plasma Hb at $t = 60$ min are shown in table XIII as a function of pH. On *t* testing, no differences between the groups were significant at the 5% level.

We conclude that alkalaemic haemolysis is unlikely to complicate extracorporeal carbon dioxide removal in humans.

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Br. J. Anaesth. (1989) **62**, 236–238

CORRESPONDENCE

NEUROMUSCULAR BLOCK IN DIAPHRAGM AND HAND

Sir,—I noted a mis-statement in a paper by Derrington and Hindocha [1]. They correctly state that it requires a greater receptor occlusion to block the twitch response in the diaphragm as opposed to the tibialis anterior muscle, but then conclude incorrectly "the results do not suggest a margin of safety in the diaphragm". Indeed, the fact that one must block *more* receptors in the diaphragm to reduce the twitch response to any given level, implies that the margin of safety in the diaphragm is greater than that in peripheral muscles.

B. E. WAUD
Worcester MA

REFERENCE

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Sir,—Thank you for the opportunity to reply to Professor Waud. Her query relates to the discussion section, where the percentage of receptors which were blocked when neuromuscular transmission was reduced by 50% was quoted directly from her paper [1]. She studied anterior tibialis muscles of the cat and compared the data with results from the diaphragm in different cats; a higher percentage of receptors needed to be blocked in the diaphragms to reduce neuromuscular transmission by 50%, the difference varying between 2.8% and 17.2%. Similar experiments in the dog showed the differences between the diaphragm and anterior tibialis ranged from −6.6% to +7.8%. We did not feel this was sufficient evidence to state that there was a clear margin of safety of neuromuscular transmission in the diaphragm; although it may be true of the cat it did not seem to be so for the dog.

M. C. DERRINGTON
Leicester

REFERENCE

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NASOTRACHEAL INTUBATION, PARANASAL SINUSITIS AND HEAD INJURIES

Sir,—Hansen and colleagues, in a prospective study, investigated the frequency of paranasal sinusitis in patients with nasotracheal intubation [1]. However, such a study should be conducted in patients without a head injury, as penetrating craniocerebral injury and bleeding into sinuses results in a CT scan positive for sinusitis.

The authors reported that all 12 patients studied showed signs of sinusitis in CT scan performed 1 or 2 days after nasotracheal intubation. In patients without head injury and intubated via the nasal route, we found an incidence of paranasal sinusitis of 38% when CT scan was performed on days 2 or 3 after intubation, and 100% in the CT scans performed on the 8th day (unpublished data). The different time of onset of fluid accumulation in the paranasal sinuses has to be attributed to the differing patients we studied in comparison with those of Hansen and colleagues. The negative preintubation CT scan does not exclude the possibility of blood accumulation soon after nasal intubation was performed. The problem of this study, that patients with cerebrovascular injury were included, might be overcome if a second group of patients were studied using oral intubation, although the two groups might not be comparable in terms of severity of head injury.

It is widely accepted that nasal intubation of the stomach and trachea should be avoided in head-injured patients [2]. Sinusitis associated with head injury probably involves blood accumulation in the paranasal sinuses, increasing the possibility of infection more than simple fluid accumulation resulting from prolonged nasotracheal intubation and blockage of the sinus drainage through the nasal ostia. The high percentage of patients who had positive cultures of nasal pus implies that possible blood accumulation in the sinuses may predispose to infection of the paranasal sinuses.

Although sinusitis was demonstrated by CT scan, the authors did not mention the frequency of involvement for each individual sinus. This is an important practical point as the possibility of sphenoid sinus involvement should not be overlooked because of the serious complications associated with sphenoid sinusitis [3]. Finally, the time needed for resolution of sinusitis following the removal of the nasotracheal tube was not investigated. Was the nasotracheal tube not removed in the presence of the nasal discharge of pus?

I believe that the time course of sinusitis and the incidence of nasal pus discharge around the tracheal tube reported in this study should not be extrapolated to nasally intubated ICU patients without head injury.

A. FASSOULAKI
Athens

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Sir,—Dr Fassoulaki is correct in pointing out that the ideal study of paranasal sinusitis in patients with nasotracheal intubation should be conducted on patients without head injury. However, we chose to include this group of patients in our study because, as a consequence of the routine in our institution, the data were readily available.

As to the use of nasotracheal intubation in neurological/neurosurgical patients, we would point out that, in Denmark, almost all patients requiring prolonged mechanical ventilation (> 24 h) undergo intubation nasotracheally. Traditionally, only patients with penetrating craniocerebral injuries undergo intubation orally. None of our patients suffered penetrating injuries. Nine of our patients had polysinusitis; of these, three had involvement of the sphenoid sinus.

The study was intended as a preliminary investigation and as such it has its flaws, for example, no control group. We believe that sinusitis is a potentionally serious complication in patients with nasotracheal intubation; consequently, more investigation is needed.

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D. Bendixen
M. Poulson
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Sønderborg

PROLONGED SUXAMETHONIUM-INDUCED NEUROMUSCULAR BLOCK ASSOCIATED WITH ORGANOPHOSPHATE POISONING

Sir,—We agree with Guillermo and Pretel [1] that asymptomatic patients with subclinical exposure to organophosphorus insecticides may develop suxamethonium apnoea. A recent case illustrates that acute subclinical exposure may be causative.

A 3-yr-old, 14-kg boy of Japanese ancestry, a recent arrival to the United States, presented for Laser microsurgery of the larynx and examination of a possible cholesteatoma of the right ear. He had tolerated three procedures in Japan for surgical ablation of juvenile papillomas; the anaesthetic regimens included suxamethonium. His immediate family history was negative for anaesthetic complications, and at the time of this procedure, he had only minor hoarseness and no stridor.

Induction of anaesthesia was by rectal methohexitone; maintenance was by halothane and oxygen during mask ventilatory support, and by methohexitone infusion with oxygen during jet-Venturi ventilation. Neuromuscular block was provided with tubocurarine 70 μg kg^{-1} (defasciculation dose) and suxamethonium 60 mg over 38 min, monitored by nerve stimulation. Upon completion of the procedure, during mask ventilatory support, the monitor continued to demonstrate no response to stimuli for 10 min. Suspecting either familial atypical plasma cholinesterase or environmental exposure to organophosphate, we questioned the father, who denied living on a farm in Japan, but admitted to having his new house treated for mice and insects 2 weeks previously. He volunteered further that the carpets on which the child played smelled strongly of the insecticides. The plasma concentration of cholinesterase at this point was 0.3 u. ml^{-1} (normal range 7.0–19.0 u. ml^{-1}). Permission was granted to proceed to tomography of the right middle ear. Anaesthesia was provided by an infusion of methohexitone and halothane was added to oxygen during the scan to minimize the extent of total i.v. anaesthesia. The child was returned to the Postoperative Care Unit; 192 min had elapsed since the suxamethonium infusion had been discontinued, and at this time he demonstrated full recovery to both twitch and tetanus. The trachea was extubated and he had no recall of the morning's events. Tests for atypical cholinesterase were incomplete because substrate was not present in an amount sufficient for the test.

Our patient returned 12 days later for surgical removal of his cholesteatoma. Serum cholinesterase was 3.1 u. ml^{-1}, vecuronium was chosen as the neuromuscular blocker and anaesthesia was uneventful. During the interim, further investigation of the environmental exposure disclosed that the insecticides in question were chlorpyriphos, a common organophosphate, and propetamphos, a potentially toxic organophosphate in restricted use.

Whilst the case is based on circumstantial evidence, it seems likely that the insecticides were responsible for precipitating the suxamethonium apnoea.

D. B. Weeks
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Winston-Salem, North Carolina

REFERENCE

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MEASUREMENT OF TRANSDIAPHRAGMATIC PRESSURE

Sir,—I read with interest the article by Derrington and Hindocha [1]. In 1964, Milic-Emili reported that the placement of an oesophageal balloon in the middle one-third of the oesophagus was associated with the most reliable measurements approximating to pleural pressure [2]. Drummond was correct to question the validity of the measurement of oesophageal pressure (*P*oe) to estimate pleural pressure in the supine anaesthetized patient [3].

Our study in 1983 assessed the validity of the oesophageal balloon technique in supine anaesthetized subjects [4]. We were able to show values of oesophageal pressure/mouth pressure (*P*oe/*P*m) within 10 % of unity in all patients, but not by blindly positioning the balloon at the middle one-third of the oesophagus Indeed, our study showed very clearly that, unless *P*m and *P*oe were compared during an occlusion test for individual patients and the balloon was positioned where a ratio close to unity was obtained, the technique to estimate pleural pressure was not acceptable. It was possible, in all subjects, to position the balloon optimally so that the Δ*P*oe/Δ*P*m (Δ*P*oe/Δ*P*t) ratio amounted to 0.98 (SD 0.03).

This simple occlusion test to validate the balloon position is not mentioned by Derrington and Hindocha and so the assumption cannot be made that the oesophageal balloon pressure will approximate reliably to pleural pressure. Transdiaphragmatic pressure (*P*di) values in this study can, therefore, be considered inaccurate. It may be valid to observe relative changes in *P*di within one patient.

B. Higgs
London

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Sir,—It is true that we did not perform the occlusion test on placement of the oesophageal balloon to validate the measurement of pleural pressure. It is also true that accurate measurement of pleural pressure is required to obtain values for lung compliance and resistance.

I fail to understand how this validation test would affect either our value for the height of the diaphragm twitch from its baseline at FRC, or the results of our studies using neuromuscular blocking drugs. What is important is that phrenic stimulation was supramaximal and this was confirmed by the fact that our values for transdiaphragmatic pressure were comparable in magnitude to those obtained by other workers.

M. C. DERRINGTON
Leicester

Br. J. Anaesth. (1989), **62**, 239

BOOK REVIEWS

Intravenous Anaesthesia, 2nd Edn. By J. W. Dundee and G. M. Wyant. Published by Churchill Livingstone, Edinburgh and London. Pp. 358; illustrated; indexed. Price £50.00.

Any new edition of a standard text book should be reviewed carefully. This text is no exception. In the 14 years since the previous edition, we have seen the departure of propanidid and Althesin, the non-arrival of minaxolone citrate, a reformulation of di-isopropyl phenol (Diprivan), and considerable doubts raised on the concept of suppression of the neuroendocrine responses to anaesthesia and surgery. Thus it is time, indeed, for the welcome appearance of this volume. In essence, the reader cannot but admire the vast contribution made by Professor Dundee and his various colleagues to the development and clinical assessment of both new and old i.v. agents.

Each of the 19 chapters is well referenced, although some are poorly selected and fail to discriminate between reports and anecdotal tales, and well controlled studies. This is always a problem—as the former often describe in detail the adverse or side-effects of drugs.

Of the individual chapters, I shall comment on only a few. That on general pharmacokinetics of the single i.v. dose gives a splendid acount in non-mathematical terms that most readers will easily grasp. However, its extension into discussing the kinetics of continuous infusion anaesthesia is not so all-embracing. It does not answer the question sought by many clinicians—why may my patient wake up if I give him a single bolus dose of a hypnotic and continue with an infusion of the drug at a fixed rate based on drug clearance and the estimated anaesthetic concentration? Indeed, the question of target drug concentrations or "therapeutic windows" is mentioned only briefly.

On the other hand, the four chapters on the kinetics and dynamics of the barbiturates (the first of the modern day i.v. agents) are well thought out and structured, and continue neatly from the earlier chapter on the history of i.v. anaesthesia. The significant contribution of John Dundee in this area of anaesthetic development can be clearly gauged from the extensive citation of his department among the references quoted. The chapter on propofol is slightly disappointing; the author has failed to differentiate clearly between data gleaned from the previous Cremophor formulation, and the present emulsion. One major problem for all authors is whether papers forming part of Symposia Proceedings (often sponsored by the Pharmaceutical House concerned) should be quoted as references in standard textbooks. Much of the data in these papers does not originate from randomly allocated, well controlled, double-blind studies; it would seem better to quote only those studies of the properties of a drug appearing in the truly peer-reviewed journals. This chapter and some others lack data relating drug concentrations and dynamic effects—the desired end result of any kinetic study.

The role of opioids in i.v. anaesthesia (either as sole agents or as part of a balanced anaesthetic technique) has been reviewed well and referenced by Jim Bovill. Unfortunately, some of the other areas of i.v. anaesthesia are thinly covered. Infusion anaesthesia is clearly a viable alternative to the volatile agents, yet there is no mention of the concept of feedback control using the EEG—an endpoint to which all dynamic comparative research on the hypnotic agents must surely relate.

Despite these minor criticisms, at the cost of £50 this book must be considered as one of the current "bibles", and is a sound investment both for the trainee studying for examinations, and as an information source for the teacher. It will be sad if another 14 years pass before the next edition of this "classic" appears, as both senior authors have put together a book representing the "state of the art" as they perceive it at present. Progress moves rapidly. One of the virtues of this volume is that it represents a clear attempt to relate together clinical observations and scientific data—not achieved easily by the non-clinical pharmacologist. I cannot recommend this readable book too highly. The authors deserve our congratulations on achieving their goal.

J. W. Sear

Positioning the Surgical Patient. By J. M. Anderton, R. I. Keen and R. Neave. Published by Butterworths Scientific, Guildford. Indexed, illustrated. Price £12.95.

This is a book for everyone who works in operating theatres, intensive care units, radiological suites and many other areas in hospitals. It is beautifully illustrated with line drawings—the artist is a co-author—and is extremely readable; the length is appropriate. The subject of positioning of patients held an important place some 20 years ago in textbooks of anaesthetics, but since then the overall concept of the subject has been a lost art; thus the publication of this book is especially welcome. Indeed, a consultant anaesthetist asked me last year—consequent upon the appointment of a new consultant neurosurgeon who had different ideas on patient positioning than hitherto obtained in one hospital—what the "park bench" position was. This book answers every conceivable question on patient positioning and warns of the many varied problems which may cause harm to patients. The text is comprehensive and written in a pleasant way that holds the reader's attention throughout. Each chapter is concluded with a helpful list of references which quote many recent papers as well as the classical texts.

The subject of patient safety is the most important aspect of anaesthetic practice at the present time. It is therefore very interesting (and, perhaps, something of a surprise to some) to see that the March 1988 issue of the *Newsletter* published by the Anesthesia Patient Safety Foundation carried a report which indicated that allegations related to improper positioning rank higher than those related to equipment problems. *Positioning the Surgical Patient* could not have come at a more opportune time; it is strongly recommended.

A. P. Adams

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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

PREOXYGENATION

In 1955, Hamilton and Eastwood [1] demonstrated that denitrogenation was 95% complete within 2–3 min with a subject breathing at normal tidal volumes from a circle anaesthesia system with a fresh gas flow of oxygen 5 litre min^{-1}. These studies probably led to the recommendation, found in most standard anaesthesia textbooks, that preoxygenation should last for 3–5 min before rapid-sequence induction of anaesthesia. Dillon and Darsi [2] observed significant desaturation of arterial blood during the apnoea following administration of thiopentone and they noted that administration of oxygen avoided this problem; they recommended, therefore, that induction of anaesthesia and endoscopy should be preceded by preoxygenation for 5 min. Heller and Watson [3] concluded that 3 min preoxygenation provided safe apnoea for 4 min, and that lower inspired oxygen concentrations were associated with shorter safe periods of apnoea.

Heller and Watson [4] showed subsequently that it was necessary to breathe oxygen for at least 3–4 min in order to increase Pa_{O_2} from 10.4 to more than 40 kPa. However, in patients undergoing artificial ventilation, Pa_{O_2} increased from 12.7 to more than 53 kPa within 30 s. These observations led Gold and colleagues [5] to study a technique of preoxygenation using four deep breaths taken within 30 s. Using a continuous, online polarographic technique they demonstrated, in healthy unanaesthetized patients, that Pa_{O_2} was similar after four maximal deep inspirations taken within 30 s compared with the Pa_{O_2} achieved in the same subjects after breathing 100% oxygen for 5 min at normal tidal volumes. Archer and Marx [6] found that the reduction in Pa_{O_2} during apnoea after induction of general anaesthesia was significantly greater in pregnant women than in non-pregnant controls. In some emergency situations there may not be sufficient time to allow preoxygenation for a full 3–5 min and it follows, therefore, that the four deep breaths, 30-s technique would be extremely useful if it achieved the same effect. This was confirmed in 1985 by Norris and Dewan [7], who studied maternal Pa_{O_2} in parturients before and after preoxygenation, and after tracheal intubation. They also extended their study to examinations of umbilical cord Pa_{O_2} and Apgar scores. In a somewhat complex study, they concluded that maternal Pa_{O_2} after four deep breaths was greater than that produced after 3 min breathing oxygen at normal tidal volumes.

There are many other studies of preoxygenation, but direct comparison of the results is difficult because of variation in methodology: there are differences in end-points, techniques and measuring devices. Using measurements of end-tidal nitrogen concentrations, and preoxygenation for 2–3 min without tracheal intubation, Berthoud, Read and Norman [8] concluded that a period of less than 3 min was sufficient. In an elegant study using measurement of arterial oxygen saturation before tracheal intubation, Drummond and Park [9] concluded that the presence of a "leak" around the face mask was associated with a lower arterial saturation (Sa_{O_2}), that three vital capacity breaths were associated with a greater Sa_{O_2} and that breathing air produced the lowest Sa_{O_2}. Furthermore, they suggested that obesity and not a small FEV_1 was associated with a lower Sa_{O_2}. Sellers and Rhodin [10] compared four deep breaths of oxygen with 5 min of preoxygenation at normal tidal volumes in 10 patients in the absence of tracheal intubation, and they suggested that deep breaths may not be beneficial, particularly in pregnant patients. Using continuous measurement of expired oxygen concentrations with a mass spectrometer, Russell and colleagues [11] concluded that the four vital capacity breath technique did not achieve optimal alveolar oxygenation in pregnant subjects. Using pulse oximetry, Gambee, Hertzka and Fisher [12] concluded that Sa_{O_2} decreased more rapidly after the four deep breath technique than after breathing oxygen at normal tidal volumes for 3 min. Goldberg and colleagues [13] studied preoxygenation in the morbidly obese. After four vital capacity breaths, patients exhibited a higher arterial pH and significantly lower Pa_{CO_2}, but the same Pa_{O_2} as that demonstrated by comparable patients who breathed oxygen for 3 min at normal tidal volumes.

Although the subject of preoxygenation has been extensively investigated, there is little agreement on which techniques are optimal and there are no universal recommendations. Understandably, this failure to confirm results is a manifestation of differences in experimental techniques and variations in patient populations encountered in many of the studies described above (some studies compared end-tidal nitrogen, end-tidal oxygen; some studies compared 3 min of oxygen breathing, others 5 min). Clearly, it is not possible to extrapolate from data obtained in normal healthy males to the parturient or morbidly obese patient, nor is it possible to infer change in Sa_{O_2} at the time of tracheal intubation from data obtained in patients in whom this manoeuvre was not performed.

It may be that, in the parturient and the obese patient, the reduction in functional residual capacity from a raised diaphragm is associated with atelectasis, particularly in the supine position, and that four vital capacity breaths may be valuable in re-expanding lung tissue. This hypothesis awaits investigation.

Despite the conflicting data which exist, it is possible to make several general statements:

(1) Breathing 100% oxygen before laryngoscopy and tracheal intubation leads to higher Pa_{O_2} and Sa_{O_2} values at the time of intubation than those seen after breathing air. Oxygen concentrations intermediate between 100% and 21% are associated with lower values of Pa_{O_2} at the time of tracheal intubation.

(2) The majority of studies indicate that breathing 100% oxygen for 3 min at normal tidal volumes leads to the same Pa_{O_2} values at the time of tracheal intubation as those achieved after similar breathing of 100% oxygen for 5 min.

(3) Arterial oxygen content is a more important determinant of hypoxaemia than is Pa_{O_2} [14] and, therefore, it is vital to assess the haemoglobin concentration in patients before anaesthesia.

(4) There is probably no significant difference between the Sa_{O_2} values achieved after breathing 100% oxygen for 5 min or 3 min at normal tidal volumes and the values obtained after breathing 100% oxygen with four vital capacity breaths over a period of 30 s. In an emergency, however, time will be saved with the latter.

M. I. Gold

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AIR EMBOLISM DURING TOTAL HIP REPLACEMENT: COMPARISON OF TWO SURGICAL TECHNIQUES

R. D. EVANS, M. G. A. PALAZZO AND J. W. L. ACKERS

SUMMARY

The frequency of air embolism was studied in 21 patients during total hip replacement. Two groups were examined, one having femoral shaft cement insertion by hand, the other by Exeter cement gun. Venous air embolism was common throughout the hip surgery, but was especially so during prosthesis positioning in the femoral shaft. There were fewer air emboli and cardiovascular sequelae detected in the gun-inserted cement group, and the only patients to show clinically significant cardiovascular abnormalities during insertion of cement and prosthesis were those having cement insertion by hand. We conclude that the incidence of air embolism and associated cardiovascular changes during total hip replacement may be expected to be reduced in those patients in whom a cement gun is used to place the cement.

Cardiovascular collapse is an occasional but well documented complication of the use of acrylic bone cement (polymethylmethacrylate) during hip surgery [1,2]. Although the aetiology is still uncertain, fat [3–5] or air emboli [4] and hypersensitivity to the methylmethacrylate monomer (MMM) [6–9] have been implicated.

Doppler ultrasonography is a sensitive detector of venous air embolism [10–13] and has revealed that the presence of air in the right heart is common during hip surgery [13–16]. Although small air emboli may be benign, the possible serious sequelae of right heart air lock and left sided paradoxical embolism have led to the recommendation of various manoeuvres to reduce the incidence; these include femoral shaft venting [4,17], and carbon dioxide insufflation of the shaft before insertion of cement [6].

Surgeons wish to reduce the volume of air trapped between cement and femoral shaft, so that prosthesis fixation may be improved. Many surgeons now use a long nozzled gun for the introduction of acrylic cement for this purpose. Since the introduction of this device, we have had the clinical impression that the incidence of untoward events during hip replacement surgery has decreased.

We have examined the incidence of air embolism in a double-blind prospective clinical study, comparing manual insertion of cement with insertion using a gun.

PATIENTS AND METHODS

Twenty-one ASA I or II male and female patients scheduled to undergo total hip replacement surgery gave informed consent to take part in the study, which was approved by the local Research Ethics Committee. All patients had a normal preoperative ECG and arterial pressure. They were allocated randomly to two groups: group I ($n = 9$) had cement placed into the femoral shaft manually; group II ($n = 12$) had cement placed with a gun (table I).

All patients were premedicated with diazepam by mouth 1 h before operation. Anaesthesia was induced with thiopentone 5 mg kg^{-1} and fentanyl 1 µg kg^{-1}. Tracheal intubation was facilitated with pancuronium 0.1 mg kg^{-1}, the lungs were venti-

TABLE I. *Demographic details (mean (SD))*

Cement insertion	n	Age (yr)	Weight (kg)	M:F
Manual	9	67.8 (8.9)	67.3 (12.5)	2:7
By gun	12	70.9 (9.7)	62.9 (8.8)	3:9

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lated mechanically, and anaesthesia was maintained with 66% nitrous oxide and 1% enflurane in oxygen (plus fentanyl supplements as required). All patients were monitored continuously using ECG, transduced central venous pressure (CVP) (13-gauge Abbott Drum-Cartridge catheter) via the antecubital fossa, radial arterial pressure (AP) (20-gauge Teflon catheter), end-tidal $P\text{CO}_2$ ($P\text{E}'_{\text{CO}_2}$) (Datex Normocap) and precordial Doppler ultrasound (Sonicaid). The Doppler transducer was positioned to give an optimal signal, which was usually about the 3rd right intercostal space. All monitoring except ultrasound was displayed continuously on a calibrated four-channel Lectromed chart recorder.

The patients were positioned for surgery in a lateral tilt on a horizontal table. In accordance with our normal practice, a small test dose of carbon dioxide (0.3 ml) was injected before surgery, through the central venous catheter in order to determine the best position for Doppler auscultation. In every patient the listening anaesthetist recorded noises unequivocally characteristic of air emboli, but no cardiovascular changes were noted in any patient.

Throughout the surgical procedure, Doppler sounds were monitored with headphones by an anaesthetist (R.D.E. or J.W.L.A.) who was unaware of the patient group and could not see the operation, which was performed in a Charnley tent. Characteristic sounds (loss of heart sounds, tinkling or "millwheel" type murmurs) heard through the headphones were indicated on the chart recorder using an event marker button. Another anaesthetist (M.G.A.P.) administered the anaesthetic and recorded the stages of the operation. For later analysis, the stages of the operation were defined as: (i) acetabular reaming, placement of acetabular cement and prosthesis and femoral reaming, (ii) insertion of femoral shaft cement and (iii) insertion of femoral prosthesis.

Fluid replacement consisted of crystalloid, in a volume appropriate to the calculated starvation deficit; blood loss was replaced as it occurred. Care was taken to avoid any air trapped in the i.v. infusion catheter reaching the patient.

In group I patients, acrylic cement (Simplex) was introduced into the femoral shaft by hand. The femoral shaft was vented using a 12-French gauge suction catheter. In group II patients, the same cement was introduced into the femoral shaft using an Exeter cement gun (with Howmedica disposable syringe insert) without venting. In all other details the surgical techniques were similar (anterolateral approach and Charnley prosthesis).

Following completion of the operation, the chart was analysed for recorded changes which may have been attributable to air emboli. A change of more than 10% in any of the continuously recorded variables (AP, CVP, $P\text{E}'_{\text{CO}_2}$, ECG) coincidental with Doppler evidence of air embolism was considered an acute physiological event, and is referred to as such in this paper. Data were analysed using Fisher's exact probability or the Mann–Whitney U test as appropriate. $P < 0.05$ was considered statistically significant.

RESULTS

For the purposes of statistical analysis the surgical procedure was divided into three periods.

The procedure during the first period was the same in both groups. Table II shows the number of patients in both groups that had one or more acute physiological events during this first stage. Among the 21 patients, six had an increase in systolic arterial pressure, and three of the six had a concomitant increase in central venous pressure; two of them also had ventricular extrasystoles. However, none of the 21 patients had episodes of hypotension, decreases in $P\text{E}'_{\text{CO}_2}$ or altered heart rate. No statistical difference was found between

TABLE II. *Acute physiological events consistent with air embolism during hip surgery before insertion of femoral cement (acetabular reaming, cement and prosthesis insertion; femoral reaming). Number of patients demonstrating acute changes in the recorded physiological variable (multiple changes in the same variable were counted once) in the combined groups (total* n = *21)*

ECG		Altered AP				
Altered HR	Arrhythmia	Decreased	Increased	Increased CVP	Decreased $P\text{E}'_{\text{CO}_2}$	Positive Doppler ultrasonography
0	2	0	6	3	0	14

TABLE III. *Number of patients with evidence of air embolism (acute changes in individual physiological variables: heart rate and rhythm, AP, CVP, PE'_{CO_2}, Doppler ultrasonography) during insertion of femoral cement. Each patient was scored according to the number of such physiological variables noted to change during the surgical stage (to a maximum of six variables examined†). No statistically significant difference between groups*

Cement insertion	n	Number of acute events† 6	5	4	3	2	1	0
Manual	9	1	0	1	0	2	1	4
By gun	12	0	0	0	1	1	2	8

the two study groups during this period (data not shown). Before insertion of the femoral cement, by either method, no patient required clinical intervention because of air embolism.

Table III shows the acute physiological events noted to occur during the second period (insertion of femoral cement by each method). For each patient, the number of recorded variables which changed concomitantly with Doppler evidence of air embolism were summated (to a maximum of 6, as six variables were examined; multiple changes in a single variable were counted only once). There was an increased frequency of acute physiological changes in those patients having cement inserted by hand, but this was not statistically signficant.

During the third period (positioning of the femoral head), the frequency of acute physiological events was significantly higher in those patients in whom the cement was inserted by hand ($P < 0.01$) (tables IV, V). Furthermore, positioning of the femoral prosthesis in that group was associated with a significantly greater incidence of acute physiological changes than occurred during the earlier period of cement insertion (tables III, V) ($P < 0.05$). However, this was not the case for those patients in whom the cement was inserted by gun. Following insertion of the femoral cement, no patient having cement insertion by gun required clinical intervention for air embolism.

TABLE V. *Number of patients with evidence of air embolism (acute changes in individual physiological variables: heart rate and rhythm, AP, CVP, PE'_{CO_2} Doppler ultrasonography) during insertion of femoral head prosthesis. For details see legend to table III. **Changes more frequent ($P < 0.01$) than in the other group*

Cement insertion	n	Number of acute events 6	5	4	3	2	1	0
Manual**	9	1	0	1	3	4	0	0
By gun	12	0	0	0	1	1	2	8

Three patients in whom the cement was inserted manually had clinically significant emboli requiring intervention (rapid fluid infusion, increased FI_{O_2} and reduced enflurane): one during insertion of cement and two during subsequent positioning of the prosthesis. In both groups, there was no correlation between the frequency of Doppler-detected air emboli and the side of the operation.

DISCUSSION

Air embolism during total hip replacement surgery is potentially hazardous and may occasionally be fatal [1,2,13,14,16,18]. The manoeuvres that have been suggested to reduce the incidence of air embolism, such as venting the femoral shaft [5,14,16,17], have met with limited success — a soft suction catheter may collapse from pressure exerted by the inserted prosthesis, rendering it ineffectual. Vent holes drilled in the distal femoral shaft have also been described [17].

In our study there was no episode of hypotension in either group up to the time of insertion of femoral cement. However, we recorded six acute episodes of hypertension among the 21

TABLE IV. *Acute physiological events consistent with air embolism during insertion of femoral head prosthesis. Values represent number of patients demonstrating acute changes in the recorded variable. **Significantly different from gun insertion ($P < 0.01$)*

Cement insertion	n	ECG: Altered HR	ECG: Arrhythmia	Altered AP: Decreased	Altered AP: Increased	Increased CVP	Decreased PE'_{CO_2}	Positive Doppler ultrasonography
Manual	9	2	2	6**	3	4	1	9**
By gun	12	0	0	0	2	1	0	4

patients, during the period before cement insertion, and these coincided with characteristic Doppler sounds of air embolus. This sudden hypertensive response has been recorded previously [2,6,9], and has been suggested to be neurogenic in origin [2].

Air emboli were common throughout the surgical procedure. There was a significantly increased frequency of acute physiological changes during prosthesis insertion in the patients in whom the cement was inserted manually. Abnormalities during placement of femoral cement alone, without prosthesis, were seen by Phillips, Cole and Lettin [2], who found that prosthesis insertion was not essential for the production of cardiovascular abnormalities. They suggested that femoral cement was more potent at inducing such changes than acetabular cement; they suggested further that this was caused by a side effect of the methylmethacrylate monomer, and not by air embolus. We detected cardiovascular abnormalities following insertion of cement, but before prosthesis insertion in both groups, but only in the presence of Doppler evidence of air embolism. Therefore we cannot support or refute their contention with out present data.

The most significant difference between the two groups in the number of air emboli was during positioning, and forcible hammering, of the femoral prosthesis, suggesting that more air is trapped with the manual placement of cement. Presumably, air is forced into the circulation through vascular openings in the bony medulla as a result of the high pressures generated within the distal femoral shaft during hammering. Interestingly, the three patients who became clinically compromised during the femoral cement–prosthesis procedure were all in the group in whom insertion of cement was manual, two of whom were the only subjects to show reductions in $P\text{E}'_{CO_2}$. One of these patients required intervention before insertion of the prosthesis. It would appear that venting the femoral shaft does not totally protect the patient from the effects of air embolism. This is not surprising if one considers that the cement traps air along the cylindrical circumference in addition to the blind end of the femoral shaft; voiding of all the air would thus require several vents.

During this study we were unable to show that the surgical position of the patient influenced the frequency of detection of air emboli or their sequelae. None of our patients had ECG or neurological evidence of paradoxical left sided emboli.

Doppler ultrasonography was a sensitive detector of air embolus; in decreasing order of frequency, supporting physiological evidence included arterial pressure changes, increased central venous pressure, arrhythmias, altered heart rate and decreased $P\text{E}'_{CO_2}$. Cardiovascular abnormalities were variable, increase in arterial pressure being more frequent than depression. Changes in $P\text{E}'_{CO_2}$ were a late finding in our patients.

Recently, other methods of air emboli detection have been described. These include end-tidal nitrogen [19], oesophageal Doppler ultrasonography [20] and oesophageal echocardiography [17]. Although these methods are more sensitive than precordial Doppler ultrasound, our data would suggest that such sensitivity is not required to detect clinically significant embolism.

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LOW-DOSE INTRATHECAL DIAMORPHINE ANALGESIA FOLLOWING MAJOR ORTHOPAEDIC SURGERY

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SUMMARY

In a randomized double-blind study we examined the effect of adding diamorphine 0.25 mg and 0.5 mg to intrathecal bupivacaine anaesthesia for major orthopaedic surgery. Duration of postoperative analgesia was considerably greater in patients given either doses of intrathecal diamorphine than in a control group of patients given bupivacaine alone ($P < 0.001$). However, there was no significant difference between the two diamorphine doses (0.25 mg and 0.5 mg), each providing prolonged analgesia (10.8 and 9.9 h, respectively). Although there was no evidence of late respiratory depression, the frequency of adverse effects, in particular urinary retention, nausea and vomiting, was high in both groups receiving intrathecal diamorphine.

Diamorphine is, theoretically, the opioid of choice for spinal administration. Its high lipid solubility speeds uptake into neural tissue and leads to reduced CSF concentrations, thus limiting rostral spread and the risk of respiratory depression [1]. Furthermore, its action is prolonged by rapid metabolism in neural tissue to monoacetylmorphine and morphine [2].

Clinical studies with extradural diamorphine 5 mg for postoperative analgesia following Caesarean section confirmed that it produces effective prolonged analgesia with a low incidence of adverse effects [3,4]. Intrathecal administration in doses of 1.25–2.5 mg also produces effective prolonged analgesia, but at the price of a high incidence of nausea, vomiting, urinary retention and respiratory depression [5].

CSF concentrations of morphine are much greater after intrathecal than after extradural administration; this suggests that much smaller intrathecal doses than used previously may be effective [6]. This was confirmed in a series of 245 patients given intrathecal diamorphine 0.5–1.0 mg for analgesia after major orthopaedic surgery; the incidence of adverse effects was acceptable, while analgesia was prolonged [7].

The present randomized double-blind study was designed to establish the duration of analgesia and frequency of side effects following two doses of diamorphine, 0.25 mg and 0.5 mg, administered intrathecally with bupivacaine spinal anaesthesia for major orthopaedic surgery.

SUBJECTS AND METHODS

Sixty patients (ASA categories I or II) scheduled to undergo major orthopaedic surgery (total hip or knee replacement) consented to take part in this study, which was approved by the local Hospital Ethics Committee.

Premedication consisted of diazepam 5–15 mg (depending on age and weight) by mouth 60–90 min before induction of spinal anaesthesia. On arrival in the anaesthetic room, each patient was allocated randomly to one of three groups: group A = intrathecal 0.75% bupivacaine 3 ml; group B = intrathecal 0.75% bupivacaine 3 ml plus diamorphine 0.25 mg in 0.9% sodium chloride 0.5 ml; group C = intrathecal 0.75% bupivacaine 3 ml plus diamorphine 0.5 mg in 0.9% sodium

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chloride 0.5 ml. Sodium chloride 0.9 % was used to dissolve diamorphine in order to render the solution isotonic. Although the manufacturers of diamorphine (Evans) recommend water as a solvent, it has been shown that it can be reconstituted safely in 0.9 % sodium chloride [8].

An i.v. infusion was commenced and lumbar puncture was performed at the L3 space using a 25-gauge needle through which the appropriate intrathecal drugs were administered. Arterial pressure and ECG were monitored continuously. Hartmann's solution 500 ml was administered i.v. before spinal block was performed; thereafter fluids were administered as appropriate, depending on blood loss and cardiovascular parameters. Ephedrine 7.5 mg i.v. was administered in the event of undue hypotension (systolic arterial pressure < 67 % of initial value). During operation, sedation was provided by increments of midazolam 1 mg as required. Oxygen 3 litre min^{-1} was administered throughout the procedure via a Hudson mask.

After operation, patients were assessed by a nurse observer at 4, 8, 12 and 24 h after induction of spinal anaesthesia. Although it was not possible for the same nurse to carry out all the observations on any one patient, all the nurses had been familiarized with the procedure and were drawn from a small pool of staff covering two orthopaedic wards. Both patient and nurse were unaware of the composition of the spinal injection.

Patients were asked to grade the severity of pain according to a four-point rank pain score (none, mild, moderate and severe). Independently, nurses were asked to assess quality of analgesia using a four-point scale (excellent, good, fair and poor) and degree of sedation with a three-point scale (wide-awake = 0, drowsy = 1, very drowsy = 2). In addition, rate of ventilation and the presence of adverse effects such as itching, nausea and vomiting and urinary retention were noted. The presence of such adverse effects was detected by observation and direct questioning. All patients were prescribed diamorphine 5 mg i.m. for postoperative analgesia and prochlorperazine 12.5 mg for nausea and vomiting. The times and total doses of both these drugs were recorded.

Results were analysed statistically by Student's *t* test, or Chi-squared test with Yates' correction or for trend, as appropriate.

RESULTS

The mean ages and weights of the patients (20 in each group) are shown in table I. There was no significant difference between groups with respect to dose of midazolam (mean 4–5 mg) or use of ephedrine. Duration of analgesia as measured by time from intrathecal injection until first administration of postoperative analgesic (table II) was significantly greater in both the intrathecal diamorphine groups than in the control group ($P < 0.001$). There was no significant difference between the two diamorphine groups (0.25 mg and 0.5 mg), each providing prolonged analgesia (10.8 and 9.9 h, respectively). Analgesic requirements during the first 24 h after operation (table III) were considerably lower in each of the intrathecal diamorphine groups than in the control group ($P < 0.01$), but there was no significant difference between the two doses used.

There was no significant difference between the groups with respect to sedation or quality of analgesia, as measured by either the patient's rank pain score or the nurse's independent assessment (figs 1,2).

TABLE I. *Demographic data.* * *Significant difference from each of the other two groups (Student's* t *test)* (P < *0.05*)

Analgesic regimen	Age (yr) (mean (SEM))	Weight (kg) (mean (SEM))	Type of operation: Knee replacement	Type of operation: Hip replacement
0.75 % Bupivacaine 3 ml (*n* = 20)	63 (2.1)	74.5 (2.6)*	4	16
0.75 % Bupivacaine 3 ml + diamorphine 0.25 mg (*n* = 20)	73.4 (1.7)*	66.7 (2.0)	6	14
0.75 % Bupivacaine 3 ml + diamorphine 0.5 mg (*n* = 20)	65.7 (2.8)	62.8 (3.1)	2	18

TABLE II. *Extent of analgesia assessed by the interval between completion of subarachnoid injection and first requirement for parenteral postoperative opioid. †Compared with bupivacaine alone (Student's* t *test)*

Analgesic regimen	Time to next analgesia (h) mean (SEM) [range]	†*P*
0.75 % Bupivacaine 3 ml (*n* = 20)	5.92 (0.34) [3.75–7.83]	
0.75 % Bupivacaine 3 ml + diamorphine 0.25 mg (*n* = 20)	10 85 (1.20) [5.0–24.0]	< 0 001
0.75 % Bupivacaine 3 ml + diamorphine 0.5 mg (*n* = 20)	9.92 (1.14) [4.75–24.0]	< 0.01

TABLE III. *Postoperative analgesic requirements for diamorphine 5 mg (during first 24 h). Statistical significance by Chi-squared test for trend*

No. of doses required	Group A: intrathecal bupivacaine alone	Group B: intrathecal bupivacaine + diamorphine 0.25 mg	Group C: intrathecal bupivacaine + diamorphine 0.5 mg
0	0	2	2
1	1	6	5
2	7	8	9
3	7	4	4
4	3	0	0
5	1	0	0
6	1	0	0
P (compared with group A)		< 0.001	< 0.005

There was no evidence of severe respiratory depression. Sixteen patients (80 %) of those receiving intrathecal diamorphine 0.5 mg and 14 (70 %) of those receiving 0.25 mg suffered nausea and vomiting, significantly more than the control group, in which the frequency was 40 % ($P < 0.05$) (table IV). Urinary retention was a common problem in the diamorphine groups, occurring in 75 % of patients given 0.25 mg and in 55 % of those given 0.5 mg. Itching was absent in the control group; in the combined diamorphine groups the frequency was 30 %, but this did not require treatment. No other major adverse effects were reported.

DISCUSSION

We have demonstrated that small intrathecal doses of diamorphine provide good postoperative analgesia for periods up to 24 h and that diamorphine 0.25 mg is as effective as 0.5 mg. We found no major adverse effects, but the frequency of nausea and vomiting was markedly greater in those receiving intrathecal diamorphine than in those receiving bupivacaine alone.

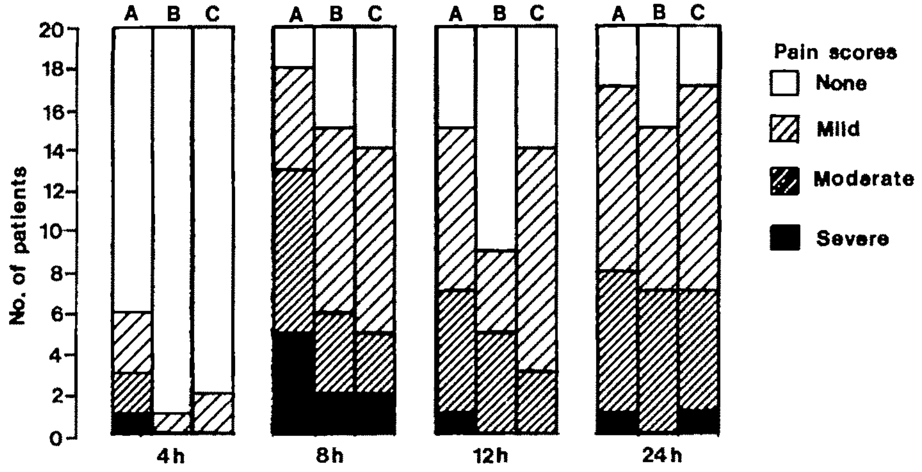

FIG. 1. Rank pain scores up to 24 h. No significant difference between groups A (intrathecal bupivacaine), B (intrathecal bupivacaine plus diamorphine 0.25 mg) and C (intrathecal bupivacaine plus diamorphine 0.5 mg).

TABLE IV. *Adverse effects (numbers of patients).* *P < 0.05 *compared with group A*

Adverse effect	Group A: intrathecal bupivacaine alone	Group B: intrathecal bupivacaine + diamorphine 0.25 mg	Group C: intrathecal bupivacaine + diamorphine 0.5 mg
Nausea and vomiting	8	14	16*
Itching	0	7*	5
Urinary retention	8	15	11
Ventilatory rate < 10 b.p.m.	0	0	0

Although there were differences between the groups, in both age and weight, it is difficult to know if this has influenced the results. However, increasing age has been shown to be associated with increased frequency of respiratory depression following spinal opioids [9]. Although this serious side effect was notably absent in our study, the greater age of patients in the group receiving diamorphine 0.25 mg may have contributed to the high incidence of adverse effects (particularly urinary retention) in this group.

In their review of extradural and intrathecal opioids, Bullingham and his colleagues [10] stated that "The basis of success with intrathecal opioids is to insert a relatively small dose of opioid into the CSF, creating a reservoir of drug to provide prolonged analgesia. In so doing, however, high local cord levels of drug are produced, far beyond those seen in normal pharmacological practice" [10]. Most intrathecal studies have used morphine which, because of its low lipid solubility, tends to linger in the CSF. This potentiates rostral spread and doses in excess of 1 mg seem to be associated with an unacceptably high incidence of adverse effects [11]. Samii, Chauvin and Viars [12] compared two doses of intrathecal morphine (0.2 mg kg^{-1} and 0.02 mg kg^{-1}) and found that, although analgesia was slightly inferior with the lower dose, the frequency of serious adverse effects, most notably respiratory depression, was considerably reduced. This has been confirmed [13] in a study using intrathecal morphine 0.25 mg and 0.1 mg, which provided prolonged pain relief after Caesarean section for 28 h and 18 h, respectively, with a small frequency of side effects and absence of respiratory depression.

The efficacy of low-dose intrathecal morphine in providing analgesia has been confirmed for major vascular surgery [14] and for major orthopaedic surgery [15–17]. However, in the most recent retrospective survey from Sweden, three patients developed delayed respiratory depression after intrathecal morphine 0.3 mg [18].

In contrast, lipophilic opioids may be safer for intrathecal use because high drug concentrations are not maintained in the mobile CSF phase [1]. Diamorphine may be the opioid of choice as it is deacetylated rapidly within the cord to morphine [2].

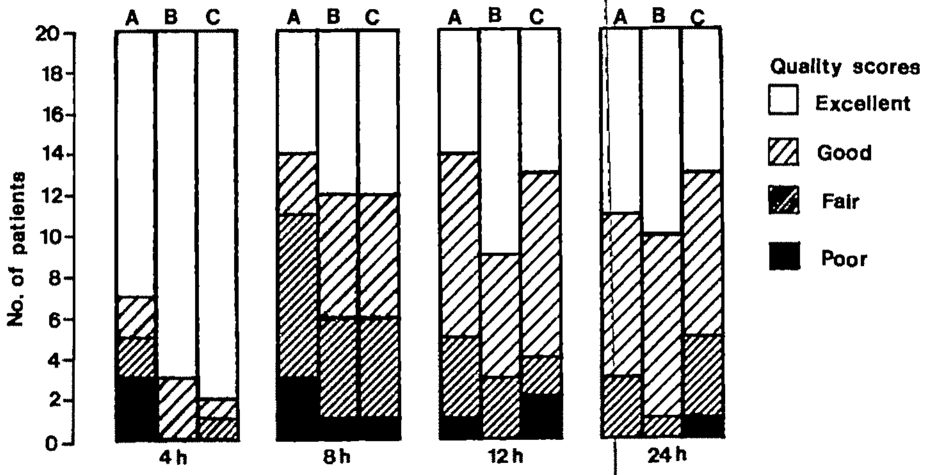

FIG. 2. Quality of analgesia scoring up to 24 h. No significant difference between groups A (intrathecal bupivacaine), B (intrathecal bupivacaine plus diamorphine 0.25 mg) and C (intrathecal bupivacaine plus diamorphine 0.5 mg).

Using diamorphine 1.25 mg and 2.5 mg in combination with intrathecal cinchocaine for patients undergoing major orthopaedic surgery, Paterson and colleagues [5] demonstrated a ceiling effect and no significant benefit from use of the greater dose. Adverse effects were frequent and four patients required naloxone to antagonize respiratory depression [5]. Comparing the analgesic effects of four different doses of intrathecal diamorphine (0.25 mg, 0.75mg, 1.5 mg and 2.5 mg), Jacobsen, Kokri and Pridie found a similar quality of analgesia in all groups [19]. Although duration of analgesia was increased with the larger doses, the higher incidence of adverse effects, particularly nausea and vomiting, was a disadvantage. However, in some patients even the higher doses did not provide "adequate" analgesia and they concluded that "sufficient quantities of opioid necessary to ensure both spinal and supraspinal effects may be required to provide the superior analgesia attributable to intradural opioid therapy". In 245 patients undergoing major orthopaedic surgery, the use of low dose intrathecal diamorphine 0.5 mg–1.0 mg provided satisfactory analgesia; 40% required no other analgesia and there was a low incidence of adverse effects [7].

In the present study we have shown that small doses of intrathecal diamorphine produce effective analgesia for major orthopaedic surgery and that diamorphine 0.25 mg provides a duration of analgesia similar to that of diamorphine 0.5 mg. This concurs with the findings of Paterson and colleagues [5] who concluded that "increasing intrathecal opiate doses above a certain level has little additional analgesic benefit".

Although no major adverse effects were encountered in our study, the frequency of minor effects was surprisingly high in the diamorphine groups despite the use of low doses. This differs markedly from the low incidence of adverse effects found in the larger study by Barron and Strong [7] (20% vomiting; 20% urinary retention) using intrathecal diamorphine in doses of 0.5 mg and 1.0 mg. Although we found no evidence of late respiratory depression, we feel that the high frequency of "minor" adverse effects, particularly nausea and vomiting, precludes the routine use of this technique, despite the prolonged analgesia it provides.

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CONTINUOUS THORACIC EXTRADURAL 0.5% BUPIVACAINE WITH OR WITHOUT MORPHINE: EFFECT ON QUALITY OF BLOCKADE, LUNG FUNCTION AND THE SURGICAL STRESS RESPONSE

N. B. SCOTT, T. MOGENSEN, D. BIGLER, C. LUND AND H. KEHLET

SUMMARY

Twenty-two patients undergoing upper abdominal surgery were entered into a randomized, double-blind study to receive extradural (T7–T8) 0.5% bupivacaine 9 ml followed by 25 mg h^{-1} with or without additional extradural morphine (bolus 4 mg plus 0.5 mg h^{-1}), for 16 h after operation. Addition of morphine was associated with total alleviation of pain, and a stable level of sensory analgesia, but not with changes in blood glucose and cortisol concentrations or postoperative impairment of lung function (PEFR, FEV_1, FVC). Two patients were withdrawn because of hypotension or respiratory depression.

The quality of blockade of afferent sensory neurones by local anaesthesia alone and consequent reduction in the surgical stress response is excellent for lower abdominal procedures, but poor for upper abdominal procedures [1–3].

It has been shown that the addition of morphine to a continuous lumbar extradural local anaesthetic infusion prevents the development of acute tolerance or tachyphylaxis [4,5]. This phenomenon occurs also with thoracic extradural anaesthesia, but it is not known if the combination of local anaesthetic and morphine prevents tachyphylaxis during segmental analgesia. By combining morphine with bupivacaine it may be possible to enhance the block and further reduce the stress response.

It is also not known if this combined infusion has a greater beneficial effect on postoperative pulmonary dysfunction than that produced by extradural local anaesthetics alone.

The purpose of this study was to compare the effect of combined thoracic extradural 0.5% bupivacaine and morphine 5 mg h^{-1} with thoracic extradural 0.5% bupivacaine alone on pain, pulmonary function, the stress response and regression of analgesia.

PATIENTS AND METHODS

Twenty patients about to undergo upper abdominal surgery gave informed consent to the study, which was approved by the local Ethics Committee. The patients were randomly allocated to one of two extradural regimens. The extradural infusions were prepared by independent members of the medical or nursing staff and the contents were unknown to the investigators or patients until the study was completed.

Anaesthesia comprised premedication with diazepam 0.2 mg kg^{-1} by mouth 1 h before operation and induction with thiopentone 2–5 mg kg^{-1} followed by suxamethonium 1.5 mg kg^{-1} after precurarization with pancuronium 1 mg. Anaesthesia was maintained using 66% nitrous oxide and 0.5–1% halothane in oxygen with pancuronium as required. Before induction of anaesthesia an extradural catheter (Portex) was introduced into the T7–T8 intervertebral space and a test dose of 0.5% bupivacaine 2 ml was given, followed by 0.5% bupivacaine 7 ml. Thirty minutes later, a "blind" bolus of saline 4 ml (group B) or morphine 4 ml (4 mg) (group

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B+M) was given extradurally. The patients then received 0.5% bupivacaine (group B) or 0.5% bupivacaine 25 mg h^{-1} plus morphine 0.5 mg h^{-1} (group B+M), to a total volume of 6 ml h^{-1}. Patients with endocrine disease were excluded from the study and the use of carbohydrate infusions was avoided during the period of investigation.

The operations in group B were three cholecystectomy, one choledocholithotomy, two explorative laparotomy, one splenectomy, one partial gastrectomy, one Roux-Y choledochoenterostomy and one duodenoplasty. In group B+M there were two cholecystectomy, one partial gastrectomy, one gastroentero-anastomosis, three explorative laparotomy, one cystogastrostomy, one jejunal resection and one right hemicolectomy.

Measurements

On the day before operation, pulmonary function was assessed by measurement of forced vital capacity (FVC) and forced expiratory volume in the first 1 s (FEV_1) using a Vitalograph. Peak expiratory flow rate (PEFR) was measured using a mini Wright's respirometer. The intra-individual coefficient of variation was less than 10% (unpublished). On the day of surgery, baseline serum glucose and cortisol concentration were measured and the patient instructed on the 5-point scale of pain assessment (0 = no pain; 1 = slight; 2 = moderate; 3 = severe; 4 = unbearable pain). Every 2 h throughout the study period, these variables were measured, together with the dermatomal level of the extradural block, using sensation of pinprick. Pain was determined at rest. Pulmonary function was assessed every 4 h.

If the pain score increased to more than 2 or anaesthesia to pinprick regressed by five or more spinal segments, the extradural infusion was stopped in that patient and no further measurements were made. Otherwise the infusion was continued for 16 h. Two patients entered into the study had to be withdrawn in the early postoperative period. One had hypotension, the other respiratory depression and both required active treatment (vasopressors and naloxone) which might have influenced the results. The infusion regimen used was unknown to the observers and it was therefore justifiable to replace those subjects by two additional patients, still in a blind manner. Both withdrawn patients had been in the B+M group.

Statistics

Data were analysed using Fisher's exact test or Student's *t* test, as appropriate. $P < 0.05$ was taken as significant.

RESULTS

Groups B and B+M were comparable with regard to age (53 (SD) 6 and 63 (5) yr, respectively), sex (M:F, 4:6 and 5:5), body weight (61 (4) and 64 (3) kg) and duration of operation (118 (43) and 167 (26) min). All patients had a sensory level of analgesia from at least T4 to T10. Both regimens provided excellent analgesia with low pain scores and stable sensory analgesia to pinprick in the initial postoperative period (fig. 1). However, with the bupivacaine infusion only four patients remained pain free and with a stable block for the entire study period, compared with all 10 patients who received the bupivacaine and morphine infusion ($P < 0.05$).

Both groups were free from lower limb paralysis after initial recovery from general anaesthesia. There was an increase in plasma concentrations of cortisol and glucose in the postoperative period, but no significant difference between the two

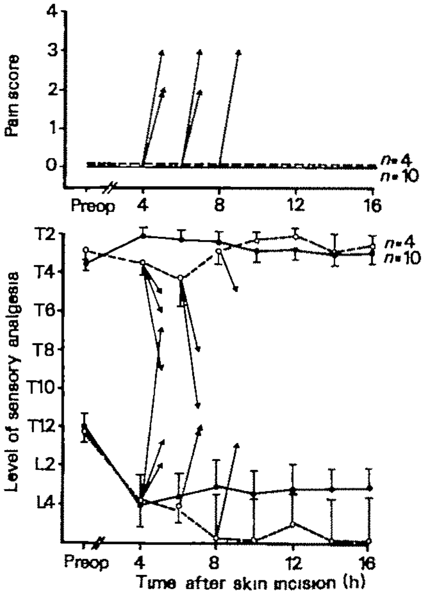

FIG. 1. Pain scores and level of sensory analgesia in patients receiving extradural bupivacaine ($n = 10$) (---) or extradural bupivacaine plus morphine ($n = 10$) (——) during upper abdominal surgery.

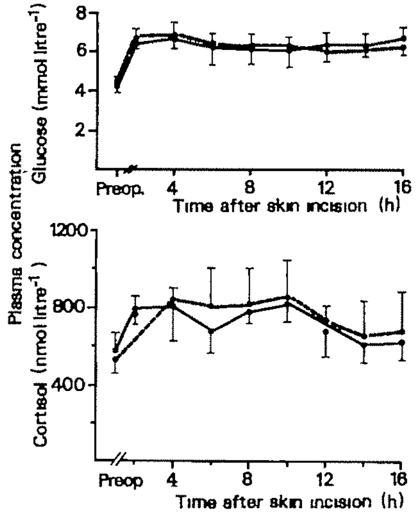

FIG. 2. Changes in plasma glucose and cortisol concentrations in patients receiving extradural bupivacaine ($n = 10$) (---) or extradural bupivacaine plus morphine ($n = 10$) (——) during upper abdominal surgery.

groups (fig. 2). PEFR, FVC and FEV_1 were all reduced ($P < 0.05$) by 40–50% throughout the study (fig. 3), but there was no significant difference between the two groups.

DISCUSSION

Our data demonstrate that the use of a continuous infusion of bupivacaine at a constant rate provides excellent analgesia. However, there was a considerable attenuation of effect with time. In only four of 10 patients did analgesia last 16 h. When morphine was added to the infusion, analgesia continued for at least 16 h in all patients in the group.

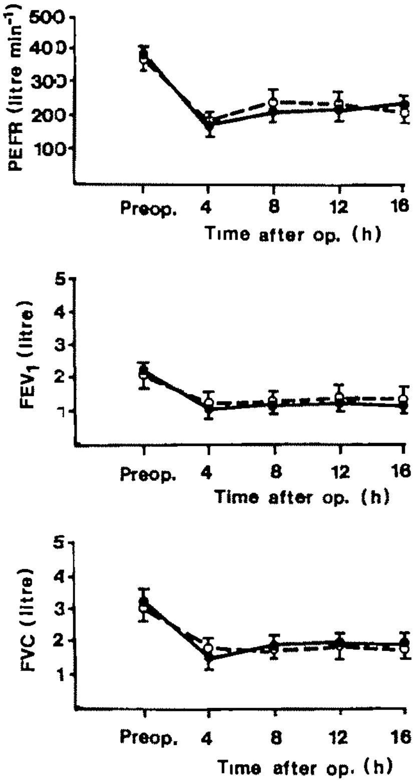

FIG 3. Changes in peak expiratory flow rate (PEFR), forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FEV) in patients receiving extradural bupivacaine ($n = 10$) (---) or extradural bupivacaine plus morphine ($n = 10$) (——) during upper abdominal surgery.

Previous studies also have demonstrated that morphine enhances and prolongs the block achieved by bupivacaine [4,5], but the mechanism of this effect is unknown. Recent experimental studies have suggested one possible explanation. Injury leads to a state of pain hypersensitivity by decreasing nociceptive thresholds peripherally and in the spinal cord [6] and the spinal dorsal column receptive fields enlarge with time [7]. It seems reasonable to deduce that spinal nerve blockade diminishes with time in the presence of unaltered local anaesthetic doses because of the resulting competitive increase in afferent input. Morphine is known to activate descending inhibitory pathways and is also effective within the dorsal horn. The resulting inhibition of nociceptive transmission may therefore restore and maintain sensory levels of analgesia, as shown in this and our previous study [5].

We failed to demonstrate any significant reduction in the glucose and cortisol responses using extradural analgesia, which is consistent with most other studies on upper abdominal surgery [1]. However, in many of the other studies, details of both the spread and duration of anaesthesia are incomplete, and very few studies document the degree of pain relief by subjective assessment. As pain is believed to contribute to, but not to precipitate, the metabolic response, such details should be documented to allow uniform interpretation of results.

There are two possible explanations of the failure to block stress responses. First, the anatomy and physiology of intraperitoneal afferent pathways are too diffuse, and afferents in the sympathetic chain synapse throughout its length before passing to the spinal cord [8], allowing stimuli to pass above and below a segmental blockade to the spinal cord. In addition, the relative extent of sympathetic block and somatosensory block during spinal and extradural analgesia with local anaesthetics is controversial [1,9]. Second, our combined regimen may not cause total afferent somatic block. Neither thoracic extradural 0.5% bupivacaine [2] nor extradural morphine [10] provides a total block of fast-conducting nerve fibres, but no studies are available for a combined regimen.

The pathophysiology of postoperative pulmonary dysfunction is complex and multifactorial [11]. The finding that near-total analgesia with extradural morphine has no effect on several tests of pulmonary function after surgery has suggested a mechanism which is not dependent on pain [12,13]. Whilst mechanical factors are clearly important [14], there may also be a neurohumoral component. Thus extradural local anaesthesia significantly improves pulmonary dysfunction [15–18]. However, our study has shown a greater than expected decrease in respiratory variables in the bupivacaine-alone group compared with other studies, and no benefit from total pain relief provided by the combined regimen. It may be that diaphragmatic and intercostal muscle paralysis was greater with the high concentrations we used, although it has been found that a sensory block from T1 to T5 with 0.5% bupivacaine 5 ml in normal individuals had little effect on lung function [19].

Two patients who received morphine extradurally were removed from the study because of hypotension and respiratory depression. We consider that the dose of morphine we used was too great to be recommended treatment. However, a low-dose regimen with approximately 4 ml h^{-1} of 0.1% bupivacaine and morphine 0.1 mg ml^{-1} did not provide total pain relief after thoracotomy [20]. Recent studies suggest that a combination of a non-steroid anti-inflammatory agent (indomethacin) with an intermediate dose regimen of extradural morphine and bupivacaine may be very effective for post-cholecystectomy pain [21].

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ELECTROACUPUNCTURE AND POSTOPERATIVE PAIN

P. A. CHRISTENSEN, M. NORENG, P. E. ANDERSEN
AND J. W. NIELSEN

SUMMARY

We studied 20 otherwise healthy women undergoing lower abdominal surgery. Immediately after wound closure, while still anaesthetized, they received either electroacupuncture (EA) or no further treatment. They were allowed pethidine for postoperative analgesia by patient-controlled infusion pump. Signs of postoperative distress (pain, nausea, drowsiness) were evaluated after 2 and 6 h by visual analogue scale scores. The group receiving EA consumed half the quantity of pethidine as that used used by the no treatment group. Two patients in the EA group had no postoperative analgesia in the first 2 h. There was no difference in the assessments of postoperative distress between groups. No patient was aware of having received EA or not.

Since Melzack and Wall introduced the gate control theory in 1965, interest in different forms of electroanalgesia (acupuncture and transcutaneous nerve stimulation) has been considerable. However, there are few clinical research studies to demonstrate any efficacy of these techniques [1,2]. As a result, the British Medical Association stressed, in the *Report of the Board of Science and Education on Alternative Therapy* in 1986, the need for controlled studies of alternative therapies.

Martelete and Fiori showed that patients treated after operation in the recovery room with electroacupuncture (EA) needed half the quantity of opioid to control pain as a group not receiving EA [2]. However, this study possessed two major flaws: lack of placebo control and absence of objective assessment of pain [3].

The present study was designed to eliminate the need for a placebo control. Patient controlled analgesia was used for objective assessment of pain.

PATIENTS AND METHODS

We studied 20 otherwise healthy women (median age 41.5 yr (range 22–52)) admitted to hospital for elective hysterectomy, salpingo-oophorectomy or operation for tubal infertility. The investigation was carried out as a patient-blinded randomized study with the performing nurse-anaesthetist blinded as well. The study was approved by the local Human Investigation Committee, and informed consent was obtained from all patients.

On the day before operation, weight, arterial pressure, heart rate and ventilatory frequency were recorded. The patient-controlled analgesia device (Prominject, Pharmacia) was demonstrated [4–6].

The Prominject is a microprocessor-controlled programmable infusion pump for parenteral administration of drugs. It possesses a dose–time memory and built-in printer. It is possible to program the infusion pump to inject defined doses when the patient presses a hand-held button. The size of the dose, and the duration of the smallest interval allowed between doses, is set in advance by the physician.

All patients were premedicated with apozepam 0.2 mg kg^{-1} by mouth 2 h before surgery. When the patient arrived in the theatre holding area, standard monitoring devices were applied. The acupuncture loci were identified and marked in all patients. An i.v. infusion of 0.9 % sodium chloride was begun. Following administration of pethidine 1 mg kg^{-1} i.v., sleep was induced with thiopentone

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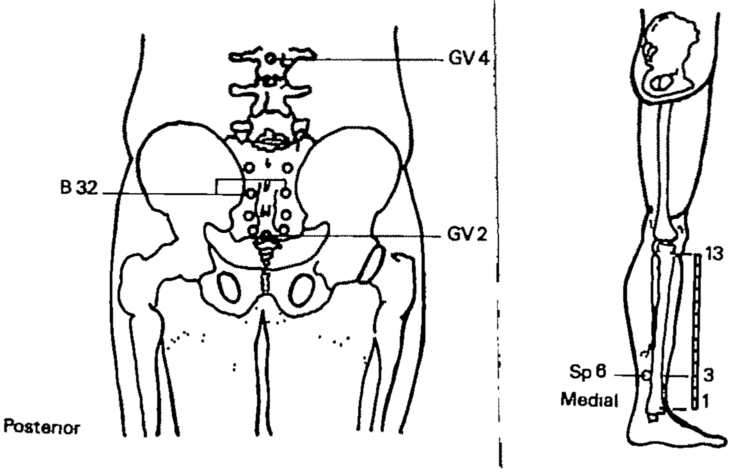

FIG. 1. Acupuncture loci. Meridian number, Chinese name and anatomical localization. GV2 = Govenor vessel 2, *Jao-Iu*, in the dosal midline between the coccyx and sacrum; GV4 = Govenor vessel 4, *Ming-Men*, in the dorsal midline below the spinal process of the 2nd lumbar vertebra: B32 = Bladder 32, *Ciliao*, bilaterally in the second sacral foramen: Sp6 = Spleen 6, *Sanjiniao*, bilaterally on the medial edge of the tibia, four fingerwidths above the tip of the internal malleolus.

4–6 mg kg^{-1} and tracheal intubation was facilitated by administration of atracurium. Ventilation was controlled manually and anaesthesia was maintained with 70% nitrous oxide in oxygen supplemented with increments of pethidine and thiopentone at the discretion of the nurse-anaesthetist.

At the time of wound closure, the patients were allocated to two groups by means of the Giegy random number table. Group ACP+ received acupuncture as described below, and group ACP− no further treatment.

All operations utilized lower abdominal incisions and all patients received sodium chloride 1–2 litre; blood loss exceeding 500 ml was replaced with whole blood.

Electroacupuncture

The loci were selected from standardized acupuncture formulae for anaesthesia in hysterectomy (fig. 1) [7–9]. The four loci on the back were localized after needle insertion. The two loci on the leg were identified finally by use of the Multiple Electronic Acupunctoscope, WC-10 R, using a hand-held probe [10]. After bandage placement the patients were placed on their side, while still anaesthetized after completion of surgery. Sterile transparent dressings (Tegaderm) were placed over each locus. The needles were inserted to the prescribed depth for each locus, then bent back against the plastic and taped in place. A constant current source was connected and the patients were returned to the supine position. Electroacupuncture was given with the following variables: pulse width 320 μs, approximately 12 V, chain frequencies of 10 and 100 Hz [11]. The acupuncture needles were 10 cm long, 30-gauge, sterilized solid stainless steel needles. They were removed after treatment. During the period of acupuncture, anaesthesia was maintained with 70% nitrous oxide in oxygen.

Upon their arrival in the recovery room, the programmed infusion pump was connected to all patients via the existing infusion of 5% glucose. Recordings of arterial pressure, heart rate and ventilatory frequency were made every 30 min for the first 2 h and thereafter at hourly intervals. Inspired oxygen concentration was increased by the use of nasal catheters with a flow of oxygen 3 litre min^{-1}.

The infusion pump was programmed to deliver 20 mg of pethidine in the first 2 h and 10 mg in the last 4 h, when the patient activated the hand-held press button. The smallest interval allowed between doses was set at 5 min. Each self-administered dose was registered on a time recorder. The nurses in the recovery room were not aware of the group to which the patients had been allocated. After 2 h the patient was asked to complete a 100-mm, vertical visual analogue scale for pain, nausea

TABLE I. *Patient data. Median values (range)*

	Age (yr)	Weight (kg)	Duration of operation (min)	Thiopentone requirement (mg)
Group ACP+ ($n = 10$) (Electroacupuncture)	41.5 (22–52)	68 (48.5–85)	142.5 (110–170)	625 (469–780)
Group ACP− ($n = 10$) (No treatment)	41.5 (27–50)	65.5 (55–69.5)	140 (105–165)	575 (432–719)

and drowsiness (0 = no trouble to 100 = worst possible). The pump was then reprogrammed to deliver pethidine 10 mg per dose.

After 6 h the recordings were repeated, the infusion pump was disconnected, and the patient was discharged to the ward.

Statistics

Statistical analyses were performed using non-parametric tests: Wilcoxon Rank Sum Test for paired differences, and Mann–Whitney Rank Sum Test for unpaired differences. $P < 0.05$ was regarded as significant.

RESULTS

The two groups were similar with regard to age, weight, duration and type of operation, and thiopentone requirement (table I). All patients were aroused easily upon arrival in the recovery room. Blood loss did not exceed 500 ml in any patient.

No problems were encountered in identifying the acupuncture loci or placing the needles.

Pethidine requirements

The pethidine requirements of each patient were recorded and grouped into three periods: during operation, during the first 2 h and during the next 4 h in the recovery room.

Median requirements of pethidine during operation were similar in both groups: 197 mg (range 130–230 mg) in group ACP+ and 195 mg (range 130–290 mg) in ACP−. One patient in group ACP+ had no need of analgesia in the recovery room and another in the same group required no analgesia during the first 2 h. Both were awake immediately after operation; one had undergone salpingo-oophorectomy and the other total hysterectomy.

Group ACP+ had a significantly smaller median opioid requirement during the first 2 h compared with group ACP− ($P = 0.007$): 60 mg (range 0–100 mg) and 100 mg (60–140), respectively (fig. 2). There was no significant difference in opioid consumption between the two groups over the subsequent 4 h ($P = 0.058$), but there was a tendency towards smaller requirements in group ACP+.

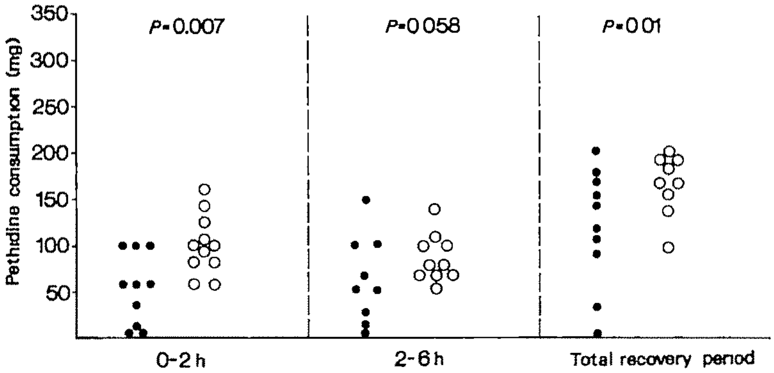

FIG. 2. Pethidine requirements of patients in group ACP+ (●) (electroacupuncture treated; $n = 10$) and group ACP− (○) (no treatment; $n = 10$) after the first 2 h, the subsequent 4 h and during the total recovery room period. P values for difference between groups are shown.

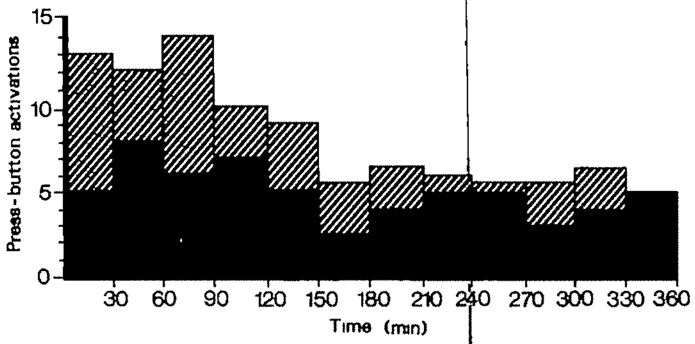

FIG. 3. Prominject press-button activations, each giving pethidine 20 mg in each group during 30-min periods in the recovery room. Black columns = group ACP+ (electroacupuncture treated; $n = 10$) cross-hatched columns = group ACP− (no treatment; $n = 10$). Two patients in group ACP+ required no analgesia for 2 and 6 h after operation.

TABLE II. *Median (range) of visual analogue scale scores for pain, drowsiness and nausea. Scale from 0 = no distress to 100 = worst possible. Both groups had the same amount of postoperative distress after 2 h and 6 h in the recovery room* ($P = 0.05$)

	Pain		Drowsiness		Nausea	
	2 h	6 h	2 h	6 h	2 h	6 h
Group ACP+ ($n = 10$) (Electroacupuncture)	48.5 (18–75)	30 (0–76)	64.5 (20–96)	41 (6–80)	0 (0–28)	13 (0–51)
Group ACP− ($n = 10$) (No treatment)	62 (42–97)	54.5 (14–74)	90.5 (33–100)	50 (0–72)	16 (0–87)	18.5 (0–60)

During the total recovery room period of 6 h, the median pethidine requirement of group ACP+ (135 mg (range 0–210 mg)), was significantly smaller than that of the group not receiving electroacupuncture (175 mg (100– 300 mg)) ($P = 0.01$) (fig. 2).

The total numbers of Prominject press-button activations, each delivering 20 mg of pethidine, during 30-min periods are shown for the two groups in figure 3. It is clear that the patients in group ACP− had a greater opioid requirement during the first 2 h than during the last 4 h. This was not found in group ACP+.

VAS scores

Visual analogue scoring revealed a similar degree of postoperative pain, nausea and drowsiness, at both 2 and 6 h ($P > 0.05$) (table II). There was a tendency towards less nausea in group ACP+, with only two patients having mild nausea, compared with six patients in group ACP−.

DISCUSSION

The results of the present study indicate an effect of electroacupuncture (EA) on postoperative pain relief after lower abdominal operations in women. There was a significant difference between the treated group (ACP+) and the control group (ACP−) during the first 2 h after operation in terms of pethidine requirements. Two patients in group ACP+ did not self-administer any pethidine during the course of the study.

The groups were comparable for subjective assessment of postoperative distress, suggesting equal compliance in use of the patient-controlled demand infusion pump system. The patients in group ACP+ received nitrous oxide for an extra 20 min after wound closure, but there is no reason to believe that this should account for better postoperative analgesia.

It is noteworthy that, in another controlled trial in which patients were treated with EA, transcutaneous nerve stimulation (TNS) or pethidine after operation, the use of EA and TNS during recovery was associated with better pain relief than pethidine alone. Furthermore, analgesia lasted longer and it increased with repeated treatment [2].

Our data suggest that the effect of EA lasted only approximately 2 h as indicated by opioid requirements. This is consistent with other studies of acupuncture and pain.

The patient-controlled demand pump was found to be satisfactory by all patients. The rate of consumption of pethidine in the ACP− group during the last 4 h was similar to that noted by Tamsen and colleagues [4] after abdominal operations.

In conclusion, the present study has demonstrated that electroacupuncture given immediately after lower abdominal surgical procedures significantly reduced opioid requirements in the first 2 h.

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We are grateful to Pharmacia for supplying the Prominject.

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NEUROMUSCULAR AND CARDIOVASCULAR EFFECTS OF DOXACURIUM IN CHILDREN ANAESTHETIZED WITH HALOTHANE†

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SUMMARY

The neuromuscular and cardiovascular effects of doxacurium chloride (BW A938U) were evaluated in 27 children (2–12 yr) anaesthetized with 1% halothane and nitrous oxide in oxygen. In nine children the incremental technique was used to establish a cumulative dose–response curve by train-of-four stimulation. The remaining children received either 30 or 50 $\mu g\ kg^{-1}$ of the drug as a single bolus. The median ED_{50} and ED_{95} of doxacurium in children were 19 and 32 $\mu g\ kg^{-1}$, respectively. No clinically significant change in heart rate or arterial pressure occurred. Following doxacurium 30 $\mu g\ kg^{-1}$ and 50 $\mu g\ kg^{-1}$, recovery to 25% of control occurred in 25 (SEM 6) and 44 (3) min, respectively. The recovery index (25–75% of control) was 27 (2) min. The duration of action of doxacurium is similar to that of tubocurarine and dimethyltubocurarine in children. Compared with adults, children seem to require more doxacurium ($\mu g\ kg^{-1}$) to achieve a comparable degree of neuromuscular depression, and they recover more rapidly.

Doxacurium chloride (BW A938U) is a new non-depolarizing neuromuscular blocking agent with a long duration of action. It is an isoquinolinium compound designated chemically as 2,2′-[succinylbis (oxytrimethylene)] bis [1,2,3,4-tetrahydro-6,7,8-trimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] dichloride.

Preclinical studies in animals and initial human studies in adults have shown that doxacurium is devoid of adverse effects. In particular, the drug enjoys an advantage over the presently available long acting neuromuscular blocking agents in that it lacks cardiovascular side effects, even in doses three times the ED_{95} in healthy patients [1,2] and two times the ED_{95} in patients with coronary disease [3,4]. The present study was undertaken to study the safety and efficacy of doxacurium in children.

PATIENTS AND METHODS

The procedure was approved by the Subcommittee on Human Studies, Committee on Research and by the Pharmacy Committee of the Massachusetts General Hospital. Parental or guardian written informed consent was obtained for each patient; in addition, consent was obtained from the older children (7 yr and over) themselves.

Twenty-seven healthy children requiring muscular relaxation for elective surgical procedures were studied. Premedication consisted of rectal methohexitone 25–30 mg kg^{-1} in children younger than eight years of age. Older children either received diazepam 0.1–0.4 mg kg^{-1} by mouth or were not premedicated. Anaesthesia was induced in the younger children with 66% nitrous oxide and halothane in oxygen. Thiopentone 5–7 mg kg^{-1} i.v. was used to induce anaesthesia in older children. Anaesthesia was maintained with 66% nitrous oxide and 1% halothane (range

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0.75–1.25%) in oxygen. The electrocardiogram, arterial pressure (Dinamap), precordial/oesophageal heart sounds, oxygen saturation, end-expired carbon dioxide concentration and oesophageal temperature were monitored.

The ulnar nerve was stimulated at the wrist via surface electrodes. Supramaximal train-of-four stimuli (2 Hz for 2 s) were generated by a Grass S88 stimulator at a rate of 0.1 Hz. The response of the adductor pollicis was recorded using a Grass FT-03 force displacement transducer and a polygraph. When arterial pressure, heart rate and neuromuscular response to ulnar nerve stimulation were stable, doxacurium was administered as a rapid i.v. bolus.

The patients were studied in three groups of nine in the following order:

Group I. In these patients, cumulative doses were given to guide administration of doxacurium. Children received incremental doses of 10 μg kg^{-1} until more than 95% twitch suppression developed. Each sequential dose was given after the peak effect of the previous dose had been achieved as indicated by three or more equal train-of-four responses. In some subjects a final incremental dose of 5 μg kg^{-1} was administered to obtain the desired degree of neuromuscular block. A cumulative dose–response curve for neuromuscular response was constructed for each patient using a log-probit method [5]. Effective doses were determined for each patient and an ED_{95} obtained for the group.

Group II. Eight patients received doxacurium 30 μg kg^{-1} as a single bolus dose. This was the approximate ED_{95} dose calculated from the first group of children. One patient in this group inadvertently received doxacurium 15 μg kg^{-1}; data from this patient were not included in the analysis.

Group III. Patients in this group received doxacurium 50 μg kg^{-1} as a bolus.

Conditions for tracheal intubation were assessed in all group II and III patients. The intubation was performed at least 5 min after administration of doxacurium, in the absence of surgical stimulation. Heart rate and arterial pressure were recorded for all patients both before administration of doxacurium began and at 1-min intervals for at least 10 min thereafter.

Clinical conditions for intubation were rated according to the ease with which the tracheal tube was passed and the patient's response. Conditions were classified as excellent when the mouth could be opened easily and no movement of the vocal cords, diaphragm, or abdominal muscles was detected during or after intubation. When the jaw muscles were relaxed but some movement of the vocal cords or abdominal muscles was detected, conditions were rated as satisfactory. When the vocal cords were moderately adducted and there was moderate coughing, the conditions were rated as poor.

If surgical conditions warranted, additional doses of doxacurium 10 μg kg^{-1} were administered as needed. The train-of-four response was monitored throughout the surgical procedure. If necessary, residual neuromuscular block was antagonized with atropine 30 μg kg^{-1} and neostigmine 60 μg kg^{-1}. Clinical neuromuscular recovery was assessed also at the end of surgery and 1 h later in the recovery room. Signs of adequate antagonism of block included effortless opening of the eyes, lifting of the head and, in co-operative patients, a grip strength commensurate with the age of the child.

The time to maximum twitch depression was determined by measuring the time from initial administration of doxacurium to the onset of maximum block. Twitch depression was expressed as percent reduction of the first twitch of the train-of-four (T1) relative to control (pre-injection). Recovery time was determined by measuring the time from administration of the last dose of doxacurium in group I patients and, in groups II and III, from initial bolus administration to return of the first twitch of the train-of-four (T1) to 5, 10, 25, 50, 75 and 95% of end-control. During recovery, the train-of-four (T4:T1) (TOF) ratios at 10, 25, 50 and 75% and before antagonism were correlated with T1 (% of control).

In nine patients, the following laboratory tests were performed before the administration of doxacurium and 12–48 h after operation: urine analysis, serum electrolyte concentrations, liver function tests and standard haematological tests.

TABLE I. *Calculated effective doses (μg kg^{-1}) of doxacurium in group I patients*

	ED_{25}	ED_{50}	ED_{75}	ED_{95}
Mean	14.4	17.6	21.7	29.4
Median	15.2	18.9	22.1	31.8
Range	8–22	9–28	10–36	12–52

Data were analysed by linear regression and correlation coefficient analysis. The mean and standard error were calculated by standard formulae. The group data were analysed by analysis of variance. Data were considered significant when $P < 0.05$.

RESULTS

The mean age (SEM) of the children studied was 5.8 (0.5) yr (range 2–12 yr) and mean weight 22 (1.9) kg (range 12–58 kg).

In group I patients, a mean dose of doxacurium 32.2 (3.3) μg kg^{-1} (range 20–50 μg kg^{-1}) was administered over 18.5 (2.6) min (range 10–36 min). The effective doses calculated from the dose–response data of these patients are summarized in table I. The average number of doxacurium doses was 3.8 (0.5).

In group II, eight patients received doxacurium 30 μg kg^{-1}. This produced 90 (4.8) % depression of T1 (range 61–100 %). Tracheal intubation was attempted 6.6 (0.4) min after injection of the drug. Conditions for intubation were considered excellent in two patients, satisfactory in five and poor in one. In the last patient the maximum neuromuscular depression was only 44 % at the time of intubation. For these eight patients mean arterial pressure and heart rate before administration of doxacurium were 67.7 (2.8) mm Hg and 90.6 (9.4) beat min^{-1}, respectively. During the following 5 min (before tracheal intubation) the maximum change in MAP was to 102.1 (6.2) % of control, while that in heart rate was to 101.8 (5.8) % of control.

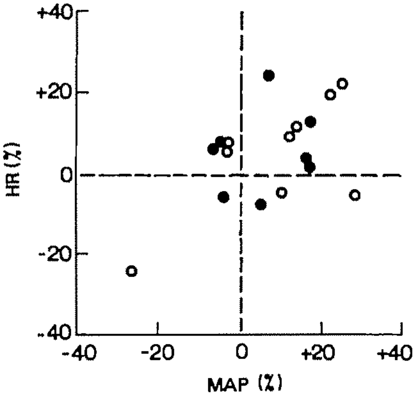

FIG. 1. The maximum percent change in heart rate (HR) and mean arterial pressure (MAP) following administration of bolus doses of doxacurium 30 μg kg^{-1} (●) or 50 μg kg^{-1} (○) before tracheal intubation.

Group III patients received doxacurium 50 μg kg^{-1} (1.7 × ED$_{95}$ dose). This dose caused 100 % twitch suppression in eight of nine patients and 98 % twitch suppression in the ninth. Tracheal intubation was attempted 5.6 (0.4) min after injection. Conditions were considered excellent in the eight patients with 100 % twitch suppression, and good in the one patient in whom the twitch was not fully ablated. In these nine patients mean arterial pressure before administration of doxacurium was 72.9 (1.8) mm Hg and the heart rate was 108.3 (6.3) beat min^{-1}; the maximum change in MAP was to 105.2 (5.6) % of control, while the change in heart rate was to 108 (6.3) % of control.

The changes in mean arterial pressure and heart rate in the first 5 min after the bolus administration of doxacurium (before tracheal intubation) were not significant at all the doses studied. Furthermore, no clinically significant individual changes were noted (fig. 1). None of the patients developed cutaneous flushing or bronchospasm.

Changes in neuromuscular variables and times of recovery from doxacurium-induced neuromuscular block are summarized in table II.

The correlation between the TOF ratio and the twitch height (T1) was highly significant ($r = 0.85$, $P < 0.001$); the intercept of the x axis was at T1 = 34.5 % and the slope of the equation was 0.92 (fig. 2).

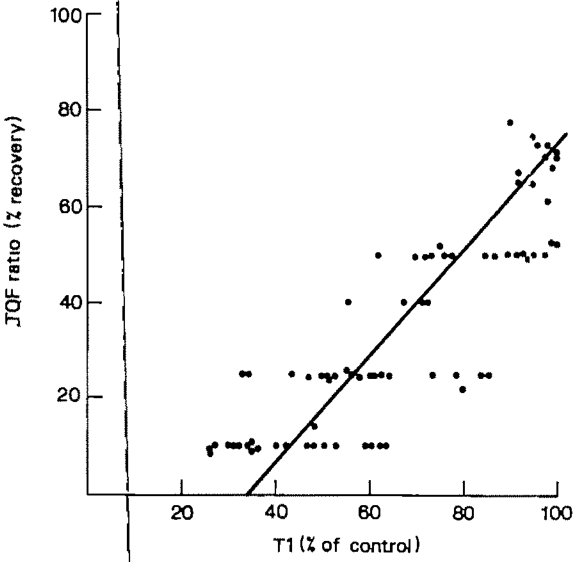

FIG. 2. Correlation between the train-of-four and the twitch response during recovery from doxacurium. Slope = 0.92; $r = 0.85$; intercept = 34.5 %.

TABLE II. *Changes in neuromuscular variables after the administration of doxacurium (mean (SEM) [range]). *In group I patients the recovery times are computed from the last dose of doxacurium. RI = Recovery index*

	Dose administered ($\mu g\ kg^{-1}$)	Inject. to max. effect (min)	Maximum block (%)	Mean recovery time of T1 from injection to % of control (min)					
				to 5%	to 25%	to 50%	to 75%	to 95%	RI
Group I* (n = 9)	32.2 (3.3) incremental	18.5 (2.6)	97.8 (0.8) [95–100]	12.8 (3) [3.5–26] $n = 8$	28.3 (3.8) [17–47] $n = 7$	37 (4.1) [27–50] $n = 6$	50.3 (6.2) [35–73] $n = 6$	68 (10.9) [42–95] $n = 4$	25.1 (3.9) [13–39] $n = 6$
Group II (n = 8)	30 bolus	6.6 (0.8) [2.2–4]	90.1 (4.8) [61–100]	19.7 (5.7) [12–31] $n = 3$	25.2 (6.2) [12–54] $n = 6$	33.8 (6.5) [14–67] $n = 7$	50.7 (8.5) [26–84] $n = 6$	51.8 (5.6) [37–62] $n = 4$	25.5 (3.2) [15–36] $n = 6$
Group III (n = 9)	50 bolus	3.2 (0.2) [2.4–3.7]	99.8 (0.22) [98–100]	29.9 (4.9) [6–59] $n = 9$	43.5 (3) [30–56] $n = 8$	63.6 (3.1) [56–70] $n = 4$	80.7 (2.7) [77–86] $n = 3$	107 (10.1) [91–126] $n = 3$	33.3 (4.4) [25–40] $n = 3$
								Mean	27.3 (2.1) $n = 15$

Neuromuscular block was antagonized in 14 patients whose surgical procedure ended before complete recovery of neuromuscular response. In these patients, twitch height at the end of surgery ranged between 22% and 92% of control (mean 53.2 (SEM 7.8)%). After a single dose of atropine 30 $\mu g\ kg^{-1}$ and neostigmine 60 $\mu g\ kg^{-1}$, twitch height recovered to 95% of control in 5.1 (1) min (range 0.2–14.5 min). In one patient the twitch response was absent at the end of surgery; diaphragmatic movements were evident, but two separate doses of antagonizing agents were needed to provide satisfactory recovery. In two other patients, T1 had recovered to more than 95% of control, but the TOF values were 44% and 54%. After administration of the standard dose of antagonizing agents, the TOF values recovered to more than 95% in 1 and 1.3 min, respectively. Three patients received atropine and neostigmine despite full twitch recovery, and seven fully recovered patients received none. There was no evidence of residual neuromuscular weakness in any patient immediately after surgery or 1 h later, when clinical evaluation was performed.

There were no clinically significant changes in the laboratory values of the nine patients who had pre- and postoperative tests. No adverse experiences occurred in any of the patients studied.

DISCUSSION

Previous studies in adults [1–4] have established that doxacurium is a safe and effective long-acting, non-depolarizing, neuromuscular blocking agent. The present study indicates that it may also be used safely in children. It does not cause any significant change in heart rate or arterial pressure, and there is no evidence of histaminergic properties in the clinical dose range. Hence, it offers advantages over the existing long-acting neuromuscular blocking agents.

Data from the present study are similar to those from an earlier one evaluating doxacurium in children anaesthetized with 0.8% end-tidal halothane [6]. In the earlier study, a median ED_{50} of 15 $\mu g\ kg^{-1}$ and an ED_{95} of 27 $\mu g\ kg^{-1}$ were found, while in our investigation the corresponding values were 19 and 32 $\mu g\ kg^{-1}$, respectively. The similarity in results is particularly striking, for we used the electromechanogram while the other investigators used the electromyogram. Both studies used train-of-four stimulation at 10-s intervals. It is interesting to note that the recovery indices (25–75 % recovery) also were comparable in the two studies (25–34 min).

Comparison with the clinical effective doses of available neuromuscular blocking agents indicates that doxacurium is the most potent, its potency exceeding even that of vecuronium [7–11]. The descending order of potency of the non-depolarizing neuromuscular blocking drugs is: doxacurium, vecuronium, pancuronium, dimethyltubocurarine, atracurium, tubocurarine, gallamine.

Markedly lower values for the ED_{50} and ED_{95} have been obtained in two earlier studies of adults under halothane anaesthesia [12–13]. With train-of-four stimulation applied at 12–15 s intervals, the ED_{50} was found to be 8.3 $\mu g\ kg^{-1}$ in one trial and 8.5 $\mu g\ kg^{-1}$ in the other, while the ED_{95} was measured at 19 and 14 $\mu g\ kg^{-1}$, respectively. This difference in requirement is similar to that observed with vecuronium, tubocurarine, pancuronium and dimethyltubocurarine [7,9,10,14]. It has been well demonstrated that children do require more of a given neuromuscular blocking agent (per kg body weight) than adults to achieve similar degrees of neuromuscular blockade.

Comparison of recovery following doxacurium in adults and children anaesthetized with halothane shows that the time from 25 % to 75 % of control twitch height is considerably shorter for children (26–33 min) than for adults (59–63 min) [15]. The time to 25 % recovery under various regimens is also shorter. Adults receiving doxacurium 23–24 $\mu g\ kg^{-1}$ during opioid anaesthesia recover to 25 % in 55 min [1,15], while those receiving 30 $\mu g\ kg^{-1}$ recover in 84 min [2]. With doxacurium 30 $\mu g\ kg^{-1}$, children during halothane anaesthesia recover to 25 % in only 25 min. Adults receiving 40 $\mu g\ kg^{-1}$ with halothane recover to 25 % in 87 min [15], while children receiving the higher dose of 50 $\mu g\ kg^{-1}$ recover in only 44 min. These data suggest that recovery from doxacurium, as with other non-depolarizing agents, is faster in children than in adults.

During our investigation, we noticed that the train-of-four recovered more slowly than the twitch response (T1). We have made similar observations previously with other blocking agents [9,11], but the difference seems to be more marked with doxacurium than with either tubocurarine or atracurium. From the correlation analysis, we observed that when the fourth twitch of the train-of-four reappeared the first twitch response had recovered to approximately 35 % of control. With tubocurarine the corresponding value was 11 % and with atracurium it was 19 % [9,11]. It is not clear if this is caused by a more pronounced prejunctional effect of doxacurium. The observation that train-of-four values correlated satisfactorily with twitch heights (T1) indicates that both single twitch and train-of-four stimulation may be used to evaluate neuromuscular block with doxacurium in children.

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RECOVERY OF NEUROMUSCULAR FUNCTION AFTER INFUSION OR INTERMITTENT BOLUS DOSES OF ATRACURIUM OR VECURONIUM

K. L. GORDON AND C. S. REILLY

SUMMARY

Neuromuscular block and postoperative recovery of grip strength and peak expiratory flow (PEF) were compared in patients receiving atracurium or vecuronium administered by continuous infusion or intermittent bolus doses. The same total dose of atracurium (0.92–0.98 mg kg^{-1}) or vecuronium (0.16–0.18 mg kg^{-1}) was given by both methods. A similar degree of neuromuscular block was attained in all groups. A control group receiving no neuromuscular blocking drugs was also studied. Grip strength and PEF were reduced significantly in all groups (< 80% of preoperative value) 15 min after operation. This was most marked following infusion of vecuronium (< 50%). Grip strength recovered in all groups in 30–60 min. PEF was still significantly less than control value at 90 min in all groups receiving neuromuscular blocking drugs.

Atracurium and vecuronium have a similar duration of action and both have been used to maintain neuromuscular block by repeat bolus doses and by infusion. The potential advantages of infusion include avoidance of both fluctuating degrees of neuromuscular block and the need to administer frequent bolus doses. There is little evidence of cumulation or delayed recovery when an infusion system is used to administer atracurium or vecuronium to healthy patients.

The dose of a drug required to produce a certain effect should be, theoretically, the same when given by boluses or by infusion, but there have been studies in which infusion of a drug increased efficacy and decreased toxicity when compared with pulsed doses to the same total dose [1]. In anaesthesic practice, however, there are few such studies comparing infusion with repeated bolus doses to the same total dose. The aim of the present investigation was to observe the degree of neuromuscular block achieved during operation and to compare the recovery of neuromuscular function after operation when atracurium or vecuronium was administered by either infusion or repeated boluses to the same total dose.

PATIENTS AND METHODS

After Ethics Committee approval, 50 healthy adult patients (ASA grades I and II) were studied. All were undergoing elective surgery for unilateral or bilateral varicose veins. They were allocated randomly to one of five study groups. Each group of 10 patients received neuromuscular blocking drugs as follows:

Group I. Atracurium bolus: an initial dose of atracurium 0.6 mg kg^{-1} followed by bolus doses of 0.15 mg kg^{-1} given 30 min after the first dose and every 20 min thereafter.

Group II. Atracurium infusion: an initial dose of atracurium 0.6 mg kg^{-1} followed by an infusion of 0.45 mg kg^{-1} h^{-1} started 10 min after the bolus dose.

Group III. Vecuronium bolus: an initial dose of vecuronium 0.1 mg kg^{-1} followed by bolus doses of 0.03 mg kg^{-1} given 30 min after the first dose and every 20 min thereafter.

Group IV. Vecuronium infusion: an initial dose of vecuronium 0.1 mg kg^{-1} followed by an in-

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fusion of 0.08 mg kg^{-1} h^{-1} started 10 min after the bolus dose.

Group V. Control group: these patients received no neuromuscular blocking drugs and maintained spontaneous ventilation.

The doses of drug were based on data sheet recommendations and were chosen to give approximately the same total dose of drug by both methods of administration over a period of 90 min: atracurium 1.2 mg kg^{-1} by both methods and vecuronium 0.22 mg kg^{-1}. The doses of atracurium and vecuronium were considered to be equipotent.

Anaesthesia

All patients received temazepam 20 mg by mouth as premedication. Anaesthesia was induced with thiopentone 4–5 mg kg^{-1} i.v. and fentanyl 100 µg and maintained with 0.5–1 % isoflurane (groups I–IV) or 1–2 % isoflurane (group V) and 66 % nitrous oxide in oxygen. Neuromuscular block was antagonized with neostigmine 2.5 mg given with atropine 1.2 mg. Postoperative analgesia (papaveretum 10–20 mg i.m.) was prescribed on demand for all patients.

Intraoperative observations

Neuromuscular transmission was monitored throughout the operation in groups I–IV using the Datex Relaxograph. The Relaxograph was calibrated for each patient following induction of anaesthesia and before administration of the neuromuscular blocking drug. The initial twitch height (T1 %) and train-of-four ratio (TOF ratio) were recorded at 5-min intervals from the administration of the initial dose. The duration of infusion, total number of increments and time from discontinuation of infusion or from last increment to administration of neostigmine were recorded. The T1 % and TOF ratio were recorded at administration of antagonizing agents and at 1-min intervals until the trachea was extubated.

Assessment of recovery of neuromuscular function

The patients' grip strength and respiratory function were measured after operation and compared with the pre-anaesthesia values. The day before surgery the patient had been visited and the study explained. At this time the patient was familiarized with the equipment to be used after operation and a practice series of three readings was taken. Grip strength of the dominant hand was measured using a compressible oil-filled cylinder with a Bourdon gauge (fig. 1). Respiratory function was measured with a spirometer (MicroMedics) and peak expiratory flow (PEF), forced expired volume in 1 s (FEV_1) and forced vital capacity (FVC) recorded. Three readings were taken for each test. PEF and FVC were measured separately. All measurements were made with the patient supine.

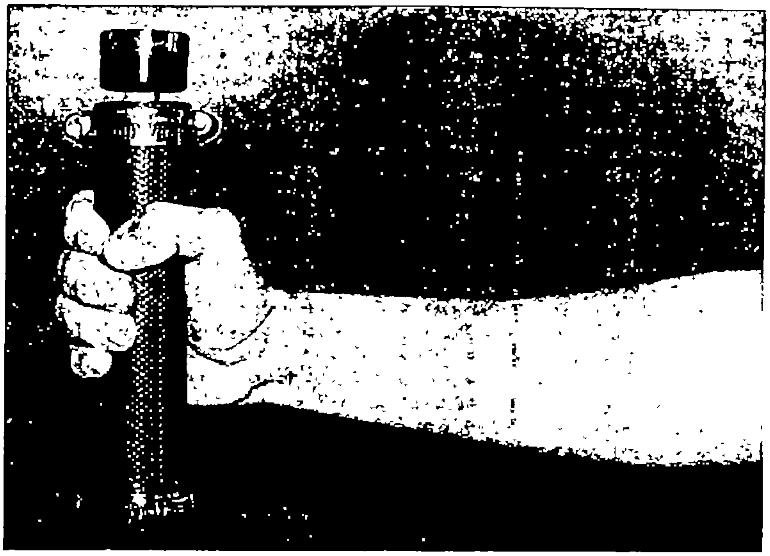

FIG. 1. Measurement of grip strength using a compressible oil-filled cylinder with a Bourdon gauge.

On the day of surgery, following premedication, the measurements were repeated. The mean value for grip strength and the best value for the respiratory variables were used as control values for the postoperative study.

Grip strength and PEF were measured on each patient at 15-min intervals for 90 min after surgery. The first measurements were made 15 min after the neostigmine–atropine was given (groups I–IV) or 15 min after discontinuation of the isoflurane (group V). FVC and FEV_1 were measured at 90 min.

All the intraoperative and postoperative observations were made by the same observer who was blinded to which agent was used, but not to the method of administration.

Data from the five groups were compared using analysis of variance (ANOVA). Where ANOVA showed significant difference between the groups, one-way analysis of variance with Tukey's HSD test was used. Where appropriate, Student's *t* test was used to compare data within each group.

RESULTS

There were no significant differences between the groups with respect to age, weight, sex or duration of operation (table I).

TABLE I. *Patient details (mean (SD))*

	Group				
	I	II	III	IV	V
Sex (M:F)	4:6	5:5	2:8	5:5	5:5
Age (yr)	48.9 (8.7)	46.2 (7.1)	42.3 (11.3)	49.7 (9.9)	45.6 (7.8)
Weight (kg)	70.8 (9.6)	72.1 (16.3)	74.0 (14.3)	80.6 (10.9)	77.2 (12.1)
Duration of anaesthesia (min)	78.2 (14.4)	77.7 (18.4)	83.2 (17.1)	77.4 (18.5)	71.8 (12.1)

The mean (SD) total dose of atracurium was 0.92 (0.11) mg kg^{-1} for group I and 0.98 (0.13) mg kg^{-1} for group II (ns). The mean total dose of vecuronium was 0.18 (0.03) mg kg^{-1} for group III and 0.16 (0.02) mg kg^{-1} for group IV (ns). The mean duration of infusion was 52.2 (18.4) min for group II and 51.8 (18.8) min for group IV (ns).

In group II the mean time from end of infusion to administration of neostigmine was 10.8 (2.2) min and in group IV it was 11.3 (2.0) min (ns).

In group I, two patients received one increment, four received two and four received three increments of atracurium (mean 2.2). In group III, one patient received one increment, three received two, and six received three increments of vecuronium (mean 2.5). There was no significant difference in the number of increments given. In group I the mean time from last increment to antagonism of block was 21.2 (5.3) min and in group III it was 21.0 (5.6) min (ns).

The median and range of T1 % for groups I–IV taken at 10-min intervals during the first 1 h of anaesthesia are shown in table II. There was no significant difference in the degree of block achieved between the two infusion groups or between the two bolus groups. As would be expected, there was more variation within the bolus dose groups than within the infusion groups.

There was no significant difference in twitch height (T1 %) at the time of reversal between the groups (table III). The time from administration of neostigmine and atropine to extubation of the

TABLE III. *Twitch height (T1 %) at time of antagonism of neuromuscular block (median and range)*

	Group			
	I	II	III	IV
T1 %	15 (5–56)	11 (0–16)	17 (3–75)	12 (3–69)

TABLE II. *Twitch height (T1 %) at 10-min intervals during operation (median and range)*

	Time (min)					
	10	20	30	40	50	60
Group I	0 (0–1)	0 (0–6)	6 (0–14)	2 (0–12)	10 (2–22)	3 (0–10)
Group II	0 (0–9)	1 (0–9)	2 (0–6)	2 (0–7)	4 (0–6)	3 (2–7)
Group III	0 (0–2)	3 (0–19)	26 (0–72)	3 (0–38)	25 (4–56)	2 (0–10)
Group IV	0 (0–3)	2 (0–12)	2 (0–8)	4 (0–9)	5 (2–10)	5 (2–6)

TABLE IV. Grip strength at 15–90 min, expressed as percentage of preoperative value (mean (SEM)). Statistically significant difference from preoperative value: *P < 0.05; **P < 0.01; ***P < 0.001

Time (min)	Group I	II	III	IV	V
15	76.4*	76.6**	63.8**	48.0***	79.5*
	(8.0)	(7.0)	(6.9)	(4.6)	(6.3)
30	84.1*	89.7	85.0*	91.4	85.6*
	(7.0)	(7.0)	(6.0)	(6.0)	(7.0)
45	89.2*	95.6	99.8	98.4	96.7
	(2.5)	(6.0)	(5.0)	(3.0)	(6.0)
60	95.9	98.9	104.3	105.3	105.1
	(4.0)	(5.0)	(7.0)	(4.0)	(4.0)
75	101.4	104.6	105.4	100.7	108.0
	(3.0)	(6.0)	(7.0)	(3.0)	(5.0)
90	100.7	107.4	106.0	104.4	111.6
	(3.0)	(6.0)	(5.0)	(3.0)	(6.0)

TABLE V. Mean PEF at 15–90 min, expressed as percentage of preoperative value (mean (SEM)). Statistically significant difference from preoperative value: *P < 0.05; **P < 0.01; ***P < 0.001

Time (min)	Group I	II	III	IV	V
15	70.0***	59.3***	57.5***	41.0***	63.1**
	(3.3)	(5.5)	(8.1)	(8.3)	(5.6)
30	76.8***	81.4**	69.4***	60.8***	78.6**
	(3.0)	(5.0)	(6.0)	(7.0)	(4.0)
45	83.7***	90.3	78.1**	74.8***	89.1
	(2.0)	(5.0)	(6.0)	(7.0)	(5.0)
60	91.6**	91.5**	83.2**	84.4**	97.2
	(2.0)	(3.5)	(4.0)	(5.0)	(3.0)
75	95.2	92.6	86.2*	85.3**	98.3
	(2.0)	(4.0)	(4.5)	(5.0)	(2.5)
90	94.2*	91.4*	88.2*	87.2*	98.9
	(2.0)	(3.0)	(4.0)	(4.0)	(3.0)

trachea, and the T1 % and TOF ratio at time of extubation were not significantly different.

Grip strength

Comparison of grip strength within each group demonstrated a significant decrease from control (preoperative) up to 45 min in group I, up to 30 min in groups III and V, but only at 15 min in groups II and IV (table IV).

The grip strength at 15 min after antagonism of blockade was significantly less ($P < 0.01$) in group IV (vecuronium infusion) (48 (4.6) % of control) compared with group I (76.4 (8.0) %), group II (76.6 (7.0) %) and group V (79.5 (6.3) %), but not with group III (63.8 (6.9) %). There were no significant differences between the groups from 30 to 90 min.

Peak expiratory flow

In group V (spontaneous ventilation) PEF was significantly reduced from control value only at 15 and 30 min ($P < 0.01$) (table V). A statistically significant reduction was still present in groups I–IV at 90 min. In the atracurium groups, PEF was greater than 90 % of control by 60 min (bolus) and 45 min (infusion). In the vecuronium groups PEF had not achieved 90 % by 90 min. This difference was not significant statistically. PEF at 15 min was significantly less ($P < 0.05$) in group IV (41.0 (8.3) %) compared with group I (70.0 (3.3) %). There were no significant differences between the groups from 30 to 90 min.

FVC and FEV_1 measured at 90 min after antagonism of blockade demonstrated no significant difference between the groups and no significant difference from the preoperative values.

There was no significant correlation between twitch height at antagonism of block and either the grip strength or PEF at 15 min. There was a significant correlation between grip strength at 15 min and PEF at 15 min ($r = 0.582$, $P < 0.001$).

Postoperative analgesia was required in nine patients (three in group I, two in each of groups II and IV and one in each of groups III and V). In all these patients analgesia was given at 30–60 min.

DISCUSSION

Administration of the same dose of neuromuscular blocking drug by infusion or by repeat bolus injections produced a similar degree of neuromuscular block during surgery. A slower initial recovery of function was found after vecuronium infusion than after vecuronium bolus.

A similar degree of block was achieved during operation between the two bolus dose groups and also between the two infusion groups. This suggests that the doses of atracurium and vecuronium used in this study were equipotent. The ratio of total doses used is in agreement with published potency ratios for atracurium and vecuronium, approximately 5:1 [2,3].

The difference in the initial recovery of both PEF and grip strength cannot be explained by differences in the time from administration of the last increment or discontinuation of the infusion until antagonism of neuromuscular block, as there was no difference between the groups in the twitch height at antagonism. However, there was no correlation between the twitch height at antagonism of block and either PEF or grip strength. This is in agreement with the findings of Noeldge and colleagues [4] who found no correlation between twitch height at reversal and the time for 25–75 % recovery of twitch height.

It has been suggested that grip strength is a more sensitive measure of residual neuromuscular block than is ventilatory function testing [5,6]. Grip strength testing requires less patient co-operation, has the advantage of being less uncomfortable than continuation of train-of-four stimulation into the postoperative period and, unlike ventilatory function testing, is not restricted by postoperative pain. The findings of our study are in agreement with a recent investigation which compared the recovery after atracurium or pancuronium and demonstrated that grip strength recovered more quickly than expiratory force [7]. This effect was more evident following pancuronium.

Some of the initial effect on grip strength and PEF must be attributed to the sedative effect of anaesthesia, as shown by the decreases in the group which received no neuromuscular block (group V). This group, however, received a higher concentration of isoflurane (1–2 %) than the other groups (0.5–1 %), who received similar concentrations of isoflurane. The differences in the clinical tests of recovery may be attributed to differences between the groups in the recovery from neuromuscular block.

The PEF at 15 min after operation was lower, but not significantly, in the groups receiving neuromuscular blocking drug by infusion than in those receiving bolus doses, despite similar twitch heights at the time of antagonism. This was more marked with vecuronium. The difference in the time course of recovery following atracurium or vecuronium may be explained in part by the differences in pharmacokinetic properties between the two drugs [8]. The difference noted between recovery from the same total dose given by infusion or by bolus dosing is more difficult to explain. Our findings are in agreement with previous studies using the 25–75 % twitch height recovery time as a measure of recovery. These studies have demonstrated no increase in this time following atracurium infusion [9,10], but a prolongation following vecuronium infusion [4] when compared with that following administration of bolus doses of each agent.

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DOUBLE BURST STIMULATION (DBS): A NEW PATTERN OF NERVE STIMULATION TO IDENTIFY RESIDUAL NEUROMUSCULAR BLOCK

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SUMMARY

We present a new pattern of nerve stimulation—double burst stimulation (DBS)—to detect residual neuromuscular block manually. The DBS consists of two short lasting, 50-Hz tetanic stimuli or bursts separated by a 750-ms interval. The response to this pattern of stimulation is two single separated muscle contractions of which the second is less than the first during non-depolarizing neuromuscular blockade. The ability to identify fade manually at different train-of-four (TOF) ratios was compared in four DBS patterns in which different numbers of impulses in the individual bursts were combined. The DBS with three impulses in each burst ($DBS_{3,3}$) was considered to be the most sensitive and the least painful and thus most suitable for clinical use. The degree of fade in TOF and $DBS_{3,3}$ was almost identical at any level of blockade (correlation coefficient 0.96), and the major post-$DBS_{3,3}$ effect was a depression of the first twitch in TOF lasting less than 15 s. It is concluded that the DBS is more sensitive than the TOF in manual detection of residual block.

The degree of residual neuromuscular block during recovery from non-depolarizing muscle relaxant drugs is evaluated normally from the response to train-of-four (TOF) nerve stimulation [1,2]. However, without quantitative recording of the evoked response it is difficult to estimate the TOF ratio. Thus when the TOF ratio has recovered to more than 0.4–0.5, fade in the response cannot be identified manually with sufficient accuracy to exclude residual curarization [3]. One reason for this may be that the two middle responses to TOF stimulation confound the estimation of the last response in relation to the first. Therefore, we postulated that a pattern of stimulation resulting in only two muscle contractions, but stressing the neuromuscular junction to the same extent as TOF stimulation, might improve the ability to identify fade manually.

The purpose of this study was to evaluate if the use of two short lasting tetanic stimuli separated by a short interval—double burst stimulation (DBS)—can be used to diagnose residual neuromuscular block manually.

MATERIAL AND METHODS

Principle of double burst stimulation

Double burst stimulation consists of two short tetanic stimulations (bursts) separated by a short interval (fig. 1). If the frequency of the tetanic stimulation is not too low (i.e. ⩾ 30–40 Hz) and if the interval between the two bursts is not too short, the response to this stimulation pattern is two single separate muscle contractions. During non-depolarizing neuromuscular block the response to the second burst of stimulation is less than that to the first, corresponding with fade to the TOF response (fig. 2).

We postulated that any difference in the two responses in DBS was felt more easily than the difference between the first and the fourth response to TOF nerve stimulation.

Different patterns of DBS can be designed from different combinations of three variables in the stimulation pattern: the frequency of tetanic stimulation, the duration of tetanic stimulation,

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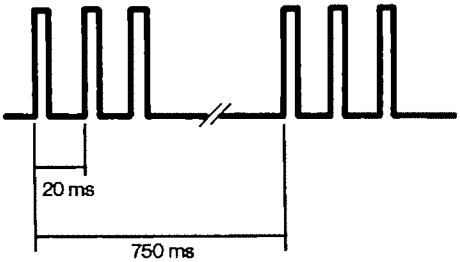

FIG. 1. Stimulation pattern in double burst stimulation (DBS). The time constants given are those of a $DBS_{3,3}$. In each burst three impulses are given at a frequency of 50 Hz (one impulse every 20 ms). The two bursts are separated by 750 ms. See text for further explanation.

and the interval separating the two tetanic stimulations. However, the number of possible combinations of these variables is restricted and the frequency of the tetanic stimulation must exceed 30–40 Hz so that the muscle response to the stimuli in the burst fuses. On the other hand, to minimize the pain caused by stimulation, a frequency as low as possible should be chosen. The duration of the bursts also has to be short (two-to-four impulses) so that the muscle response is felt as a single short lasting contraction and not as a sustained response. The duration of the muscle contraction following such bursts is approximately 400–500 ms. Therefore, to have the two muscle responses clearly separated in the DBS, the interval between the individual bursts should be longer than the 500 ms separating the impulses in the TOF.

Preliminary studies

In preliminary studies, nine different patterns of DBS were investigated (table I). On the basis of how easily fade was detected manually at different levels of block, a limited number of combinations of the variables were selected for further clinical study. It was found that the major determinant of the response to DBS was the duration of the tetanic stimulation—that is, the number of impulses and not the frequency (50 or 100 Hz) used in the bursts. Further, if identical frequencies but different durations were used, a more pronounced difference between the two responses to DBS was felt. To have the muscle contractions separated as clearly as in the TOF response, an interval of 750 ms was selected in all DBS patterns used.

TABLE I. *Different combinations of frequency and number of impulses in the first and the second burst of the DBS used in the pilot study. The interval between the bursts was 750 ms. $DBS_{3,3}$, $DBS_{4,4}$, $DBS_{3,2}$, and $DBS_{4,3}$ are indicated. See text for further explanation*

	Tetanic frequency		No. of impulses	
DBS	Burst 1	Burst 2	Burst 1	Burst 2
	100	100	2	2
	100	50	3	3
	100	50	3	2
	50	50	2	2
$DBS_{3,3}$	50	50	3	3
$DBS_{4,4}$	50	50	4	4
$DBS_{3,2}$	50	50	3	2
$DBS_{4,3}$	50	50	4	3
	50	100	3	2

Based on the results of these preliminary studies, four different patterns of DBS were selected for further clinical evaluation (table I). All the DBS patterns selected included the use of a 50-Hz tetanic stimulation. In $DBS_{3,3}$ and $DBS_{4,4}$, three and four impulses, respectively, were given in each tetanic burst. In $DBS_{3,2}$ three impulses were given in the first burst and only two in the last; in $DBS_{4,3}$ there were four and three impulses, respectively.

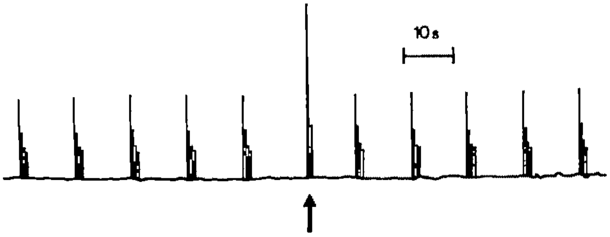

FIG. 2. Mechanical twitch recording of a $DBS_{3,3}$ (at arrow). Notice that the degree of fade in the DBS response corresponds to the degree of fade in the TOF response.

Design of the main study

We studied 41 adult patients (ASA physical status I or II) undergoing elective gynaecological or gastroenterological surgery. None of the patients suffered from neuromuscular disease or received any drug that might alter neuromuscular function. The study was approved by the local Ethics Committee, but informed consent was not obtained as the anaesthetic and monitoring procedures were those used in standard practice.

One hour after administration of diazepam 0.2 mg kg^{-1} by mouth, anaesthesia was induced with thiopentone 3–5 mg kg^{-1} i.v. and maintained with 66 % nitrous oxide and 0.75–1.5 % halothane in oxygen. Ventilation was controlled to maintain normocapnia. Tracheal intubation was performed following administration of suxamethonium 1.5 $\mathrm{mg\,kg^{-1}}$ i.v. Pancuronium 1–1.5 mg was given when necessary to maintain neuromuscular block. Following induction of anaesthesia the ulnar nerve of the arm under investigation was stimulated supramaximally at the wrist via cutaneous electrodes connected to either a Myotest nerve stimulator or a computerized unit programmed to deliver TOF stimulations and any combination of DBS. The adduction force of the resultant thumb twitch in response to TOF and DBS stimulation was measured by a force displacement transducer and recorded using a polygraph [2].

The study comprised three parts.

Part 1. Manual evaluation of DBS. The purpose of this part of the study was to investigate the four DBS patterns chosen from the pilot study in order to select the DBS with the highest sensitivity. In 24 patients the mechanical twitch was measured from one arm (the control arm) during TOF stimulation. On the other arm (the test arm) TOF stimulation was given as the basic pattern of stimulation. At regular intervals (more than every 2 min) a DBS stimulation was given in place of TOF stimulation. The four DBS ($DBS_{3,3}$, $DBS_{4,4}$, $DBS_{3,2}$, and $DBS_{4,3}$) were given in random order during spontaneous recovery of the block. The response to the selected DBS was evaluated manually by two observers without access to the TOF ratio measured in the control arm. The observers had to decide if fade was present in the DBS response.

Part 2. Relation between TOF ratio and DBS ratio recorded mechanically. The purpose of this part of the study was to establish the relationship between TOF ratios and the ratios of the DBS pattern selected in part 1. In 10 patients, paired twitch recordings of TOF and $DBS_{3,3}$ were made in one arm during spontaneous recovery of block from a TOF ratio of 0.2 to a TOF ratio of 0.8–0.9. TOF was given as the basic pattern of stimulation. At regular intervals (more than every 2 min) a DBS was given in place of TOF stimulation. The response to the last TOF stimulation preceding the $DBS_{3,3}$ was used for calculation of TOF ratio. The DBS ratio was defined as the ratio between the height of the second response in relation to that of the first.

Part 3. Decurarizing effect of $DBS_{3,3}$. The purpose of this study was to investigate a possible decurarizing effect of DBS stimulation. In seven patients, both the height of the first response in the TOF and the TOF ratio obtained from mechanical twitch recordings 3, 15 and 27 s after $DBS_{3,3}$ were compared with the twitch height and the TOF ratio of the last TOF response preceding the $DBS_{3,3}$ during spontaneous recovery of the block. TOF and DBS stimulation were given as described in part 2.

For statistical evaluation, Fisher's exact probability test, Chi-square test for two independent samples, Wilcoxon matched pairs signed ranks test, Student's *t* test and analyses of linear regression (least square methods) were used.

RESULTS

Part 1

Table II shows the number of instances in which fade was felt in the four different DBS responses at different TOF ratios. The results obtained with $DBS_{3,3}$ in the preliminary study and in part 1 were not statistically different and therefore were pooled. Thus the response to $DBS_{3,3}$, $DBS_{4,4}$, $DBS_{3,2}$, and $DBS_{4,3}$ were evaluated 199, 129, 128 and 123 times, respectively. There was no statistically significant difference between $DBS_{3,3}$ and $DBS_{4,4}$ at any TOF ratio. Significantly more examples of fade were identified with $DBS_{3,2}$ compared with $DBS_{3,3}$ when the TOF ratio was above 0.5. In the interval 0.81–0.90, a statistically significant difference was found also between $DBS_{3,3}$ and $DBS_{4,3}$. Generally, with any of the DBS selected, only few cases of fade were not felt when TOF ratio was less than 0.5. When TOF ratio had recovered to more than 0.8, fade was detected only rarely with $DBS_{3,3}$ and $DBS_{4,4}$, while many instances of fade could still be felt with $DBS_{3,2}$ and $DBS_{4,3}$. $DBS_{3,3}$ was considered to be the most useful pattern of the four DBS tested.

Part 2

For each patient a close linear relationship was found between TOF ratio and $DBS_{3,3}$ ratio. There was no significant difference between the estimated lines of regression in each patient. The observations were pooled and a common linear regression line was estimated:

$$\text{DBS ratio} = 1.07 \times \text{TOF ratio} - 0.032$$

TABLE II. *Tactile evaluation of fade in four different DBS responses. Figures indicate the number of instances in which fade was felt in relation to the total number of observations within each interval of true TOF ratios as measured mechanically. Significant differences* ($P < 0.05$) * *between* DBS$_{3,2}$ *and* DBS$_{3,3}$, *and* † *between* DBS$_{4,3}$ *and* DBS$_{3,3}$

True TOF ratio	DBS$_{3,3}$ fade/total	%	DBS$_{4,4}$ fade/total	%	DBS$_{3,2}$ fade/total	%	DBS$_{4,3}$ fade/total	%
< 0.40	39/39	100	8/8	100	14/14	100	9/9	100
0.41–0.50	24/25	96	14/14	100	7/7	100	15/17	88
0.51–0.60	15/25	60	10/21	48	18/19	95*	14/19	74
0.61–0.70	15/34	44	11/24	46	23/24	96*	17/26	65
0.71–0.80	8/33	24	8/29	28	24/28	86*	10/20	50
0.81–0.90	0/21	0	1/22	5	15/24	63*	9/21	43†
0.91–1.00	0/22	0	0/11	0	4/12	33*	0/11	0

Standard deviations of regression coefficient (slope) and of the constant (intercept) were 0.03 and 0.08, respectively (fig. 3).

Part 3

The twitch height from TOF stimulation was depressed significantly 3 s after a DBS$_{3,3}$ stimulation. However, at 15 s and 27 s the twitch had increased significantly, although these changes were very small. The TOF ratio increased significantly at 3, 15 and 27 s after DBS stimulation, although changes at 15 and 27 s were minimal (table III). The changes in both twitch height and TOF ratio following DBS$_{3,3}$ stimulation showed no relationship to the level of block at which DBS was given.

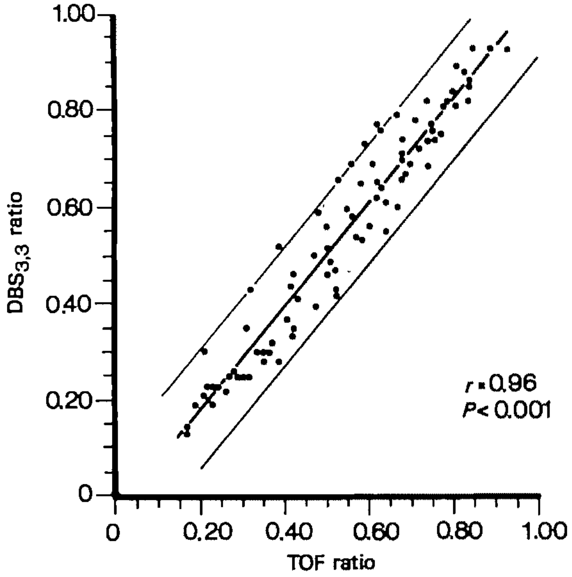

FIG. 3. Scattergram and regression line of simultaneous TOF ratios *v.* DBS$_{3,3}$ ratios as measured at the same arm. 95% confidence limits are shown.

DISCUSSION

Our results suggest that residual neuromuscular block can be detected from manual evaluation of the response to a double burst stimulation. The results also suggest that this new pattern of stimulation is more sensitive than the train-of-four method used manually.

Two of the DBS patterns chosen from the pilot study (DBS$_{3,3}$ and DBS$_{4,4}$) were found to be similar with regard to the number of cases in which fade was detected at any level of block. At TOF ratios less than 0.5, residual block was identified in almost all cases and at ratios between 0.5 and 0.7 neuromuscular block was judged not to have recovered adequately in 50% of cases. With a true TOF ratio greater than 0.7, residual block was detected only rarely with either DBS$_{3,3}$ or DBS$_{4,4}$. In DBS$_{3,2}$ and DBS$_{4,3}$ the degree of DBS fade at any given level of relaxation was enhanced artificially by reducing the number of

TABLE III. *Change in twitch height (percent of the control twitch height before injection of pancuronium) and TOF ratio (absolute changes) 3, 15 and 27 s after* DBS$_{3,3}$ *(median (SD)). All values are significantly different* ($P < 0.05$) *from the respective response to the TOF stimulation given* 12 *s before* DBS$_{3,3}$

	3 s	15 s	27 s
Twitch (%)	−4.0 (4.8)	+1.7 (1.8)	+1.1 (1.8)
TOF ratio	+0.07 (0.05)	+0.01 (0.02)	+0.01 (0.02)

impulses in the second burst compared with that of the first. This might improve the ability to identify fade manually. Indeed, significantly more cases of fade were found with DBS$_{3,2}$ compared with DBS$_{3,3}$ when the TOF ratio was greater than 0.5. The results with DBS$_{4,3}$ showed the same tendency, although no significant difference was found between DBS$_{4,3}$ and DBS$_{3,3}$. However, at TOF ratios greater than 0.7, too many cases of clinically insignificant fade were identified with both DBS$_{3,2}$ and DBS$_{4,3}$. Thus with DBS$_{3,2}$ and DBS$_{4,3}$ a false impression of persistent residual block may arise and lead eventually to unnecessary administration or overdoses of an anticholinesterase drug. Consequently, DBS$_{3,3}$ and DBS$_{4,4}$ were chosen as the most suitable and, of the two, DBS$_{3,3}$ was considered to be the least painful.

In a previous study [3] on manual evaluation of the response to TOF stimulation, a method was used similar to that in the present study. The results of the two studies suggest that, when the TOF ratio exceeds 0.4, more instances of fade can be identified with the DBS$_{3,3}$ method than with TOF. This, in combination with our observation that the degree of fade in DBS$_{3,3}$ and in TOF is similar at any level of block, supports our hypothesis that the presence of the second and third responses in TOF impede manual identification of fade. The tetanic fade and post-tetanic facilitation seen during and following, for example, a 50-Hz tetanus for 5 s is well-known [4]. However, a single stimulus is sufficient to elicit measurable fade or measurable facilitation of the following responses during neuromuscular block [5]. The degree of both depends upon the frequency with which the following stimulations are applied [5], but facilitation following a single stimulus is apparently a process of shorter duration than that leading to fade. Thus the DBS$_{3,3}$ was expected to influence the response of the succeeding TOF stimulations. A characteristic depression of the first twitch in the TOF response was observed 3 s after DBS$_{3,3}$. However, the ratio of the TOF response was increased, as the magnitude of the fourth response in the TOF was not affected. A small increase in both twitch height and TOF ratio was observed in the second and third TOF responses following DBS$_{3,3}$. These changes probably result from the slow spontaneous recovery that took place during the procedure. Thus our results suggest that the major post-DBS$_{3,3}$ effect is a depression of only the first twitch in the TOF response. However, this effect is short-lived and neither the twitch nor the ratio in the TOF response was affected when applied 15 s after DBS$_{3,3}$ stimulation.

In conclusion, residual neuromuscular block can be detected from the response to a double burst stimulation. A stimulation pattern of two bursts, each consisting of three impulses given at a frequency of 50 Hz and separated by 750 ms, seems to be the most appropriate for clinical use. The degree of fade in this DBS response and in the TOF response is similar at any level of block. However, although this new pattern of stimulation is apparently more sensitive than the TOF in manual detection of residual block, absence of manual fade in the DBS$_{3,3}$ response does not exclude residual block. Further clinical studies are needed to delineate more precisely the field of application of DBS.

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TRAIN-OF-FOUR FADE DURING ONSET AND RECOVERY OF NEUROMUSCULAR BLOCK: A STUDY IN NON-ANAESTHETIZED SUBJECTS

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SUMMARY

The actions of alcuronium, vecuronium and tubocurarine have been studied in the isolated forearms of six healthy, non-anaesthetized volunteers. The responses of adductor pollicis were measured during onset and recovery of neuromuscular block for each agent. There was a drug-related disparity between mechanomyogram (MMG) and electromyogram (EMG) measurement of the first response of the train-of-four (T1) and of the ratio of the fourth (T4) to the first response (TOF ratio). There were significantly higher T1 values for the EMG than for MMG during alcuronium blockade ($P = 0.03$). For tubocurarine, however, the relationship was reversed. The relationship between T1 and TOF ratio during onset and recovery of neuromuscular block was a hysteresis. The TOF ratio at 50% T1 was significantly higher during onset than during recovery for all three drugs, measured by MMG or EMG ($P < 0.005$). Analysis of variance of the differential fade loops failed to show a drug-related effect. We conclude that care should be taken in assuming interchangeability between MMG and EMG measurement of T1. Relationships between T1 and TOF ratio derived during recovery do not necessarily apply during onset and may lead to error in estimating the degree of muscle relaxation.

Muscle fade during train-of-four (TOF) stimulation at 2 Hz is a standard clinical method of estimating degree of neuromuscular block [1,2]. Ali and his co-workers [3] demonstrated a straight line relationship between the height of the first response of the TOF (T1) and the ratio of the fourth (T4) to the first response (TOF ratio) which is now used widely to predict residual neuromuscular block. Early studies of TOF were performed using the mechanomyogram (MMG), but electromyography (EMG) has been used increasingly as an alternative [4]. There is evidence, however, that there may be drug-related disparities between MMG and EMG recording [5]. Also, the relationship between T1 and TOF ratio may differ depending on whether neuromuscular block is being induced or is recovering [6,7]. This finding may have important implications for the clinical use of the T1/T4 relationship.

We report a study of the relationship between T1 and TOF ratio through all stages of onset and recovery of neuromuscular block using simultaneous MMG and EMG recording.

SUBJECTS AND METHODS

We studied six male service volunteers, aged 18–35 yr. All were healthy with no personal or family history of neurological disorder or allergy and no history of trauma to the forearm. The study was conducted in accordance with the recommendations of the World Health Organization guidelines for human studies [8]. Smoking and alcohol intake were restricted for 12 h before any experimental session. The response of adductor pollicis to alcuronium, vecuronium and tubocurarine was studied in each subject at 1-week intervals. The evoked compound action potential (ECAP) and muscle twitch or mechanomyogram (MMG) [9] were recorded simultaneously in the isolated forearm.

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Isolated forearm technique

The method used was based on that of Feldman and Tyrell [10]. Each subject was studied lying on a couch at an ambient room temperature of 22 °C. A suitable vein on the dorsum of the right hand was cannulated using a 21-gauge Butterfly needle (Abbott). Needle electrodes for nerve stimulation were inserted subdermally at the ulnar side of the wrist proximal to the skin crease and halfway up the forearm. The upper electrode was sited at least 10 cm proximal to the lower one. A standard anaeroid sphygmomanometer cuff was placed around the arm above the elbow. Felt pad EMG electrodes soaked in saline and covered with conducting gel were mounted into a plastic holder (Medelec type SE40) and strapped over the dorsum of the hand with the positive electrode lying over the first dorsal interosseous space and the second over the second metacarpophalangeal joint.

Trial stimuli of 0.2 ms duration and up to 140 V were given and the electrode positions adjusted to give the maximum single peak value of the ECAP. The potential applied to the stimulating electrodes was adjusted to be at least 30% above the threshold for maximum response, to ensure supramaximal stimulation. The arm with the EMG electrodes was placed into the arm frame assembly of a Myograph 2000 unit (Biometer, Copenhagen) [11]. The thumb was fixed securely into the ring of the strain gauge transducer with gauze swabs to avoid slipping from the correct right-angle position. The arm was fixed by evacuation of the surrounding air splint and the Velcro straps were tightened, taking care not to displace the EMG electrodes.

EMG recording

ECAP signals were amplified and displayed using a Medelec MS6 electromyograph through an AA6 biostable amplifier set to a bandwidth of 8–1.6 Hz. Amplifier gain was set so that the upward (negative) part of the signal covered two or three divisions of the screen. The gain was increased as the signal amplitude decreased after neuromuscular block to maintain this presentation. The linearity of the gain control of the AA6 was verified using the built-in calibration facility. Recordings of ECAP were made on light sensitive paper from the recording oscilloscope of the MS6. During the test period before administration of the neuromuscular blocker, signals were recorded first in a conventional, single sweep *x–y* mode and thereafter in gated mode which presents the single peak height as a straight line. ECAP amplitude was measured manually from the negative single peak height. At the end of each experiment further recordings of ECAP were made using the conventional *x–y* plot to compare the final waveform shape with the original. Gross movement artefacts in the EMG electrodes during recording produce a distortion of the ECAP and a consequent error in measuring the single peak height. No results were rejected because of waveform distortion in the 18 recordings made during the study.

MMG recording

MMG signals were recorded graphically and digitally from the Myograph 2000 system. The force–displacement transducer used records reliably over a range of 0–15 kg [11]. The preload applied to the thumb was set to 0.3 kg, using the adjusting ring of the transducer. After evacuation of the splint this value was observed closely during the period of initial stimulation. Stability was gained usually after 2 or 3 min during which the subjects became used to the nerve stimulation and the associated muscle twitches.

Experimental procedure

Each subject was studied double-blind at 1-week intervals when alcuronium 1.5 mg, vecuronium 0.6 mg or tubocurarine 5 mg was used. The order of administration of the drugs was randomized. The doses were determined from pilot studies to provide approximate equivalent relaxation in the isolated forearm, and recovery, within a period of 1 h. Trains-of-four at 2 Hz were generated using the Myotest stimulator which triggers the Myograph recording unit inductively. The Myotest and MS6 units were synchronized by taking the output of the Myotest stimulator and passing it via a Zenner diode to the MS6.

After the isolated forearm arrangement was set up and the response to pulses at 1 Hz was tested, control values of T1 and TOF ratio were measured. Five TOF stimuli were delivered during each 1 min at this time, allowing 10 s between the finish of one train and the start of the next. At time zero the cuff was inflated to 250 mm Hg and blocking drug (diluted in 40 ml of normal saline) was administered i.v. over a period of 40 s. The cuff was left inflated for 3 min, during which time TOF stimuli continued at 10-s intervals.

After 3 min the cuff was released and the same pattern of stimulation continued up to 10 min. After this time, recordings were made at 1-min intervals until return of MMG and EMG to control values or to a maximum time of 50 min after inflation of the cuff.

The isolated forearm technique was tolerated well in all subjects and there were no clinical sequelae, with the exception of occasional slight blurring of vision following release of the cuff and evidence of local histamine release in some subjects to whom tubocurarine was administered.

In order to check the distribution of the saline containing the neuromuscular blocking drug in the forearm, one subject was studied separately using technetium-99 as label. Two different injection sites were examined on two occasions. In the right arm, the ^{99}Tc-labelled saline was injected through the dorsum of the hand and in the left the injection site was approximately 15 cm proximal to the wrist crease. The tourniquet was inflated for 3 min and the spread of the labelled saline monitored using a gamma camera. Injection through the hand produced acceptably even distribution of the isotope through the forearm, whereas injection through the forearm site produced some concentration in the nearby superficial tissues and uneven distribution. For this reason the hand route was chosen.

Statistical methods

MMG and EMG recordings for each agent in the six subjects were analysed using the paired *t* test and two-way analysis of variance [12]. Correlations between MMG and EMG measurements of TOF ratio and T1 were made across all subjects using a method of weighted averages [13].

RESULTS

Pattern of T1 and TOF ratio responses

The form of responses obtained from the six subjects studied is illustrated in figure 1, which shows plots of MMG and EMG measurements of T1 and TOF ratio against time from one representative subject (no. 4). Table I shows two variables ($T1_{min}$—the lowest recorded value as a percentage of the control—and $T1_{rec}$—the time for T1 to recover from 25 % to 75 % of the control value) derived from the original data for all six subjects.

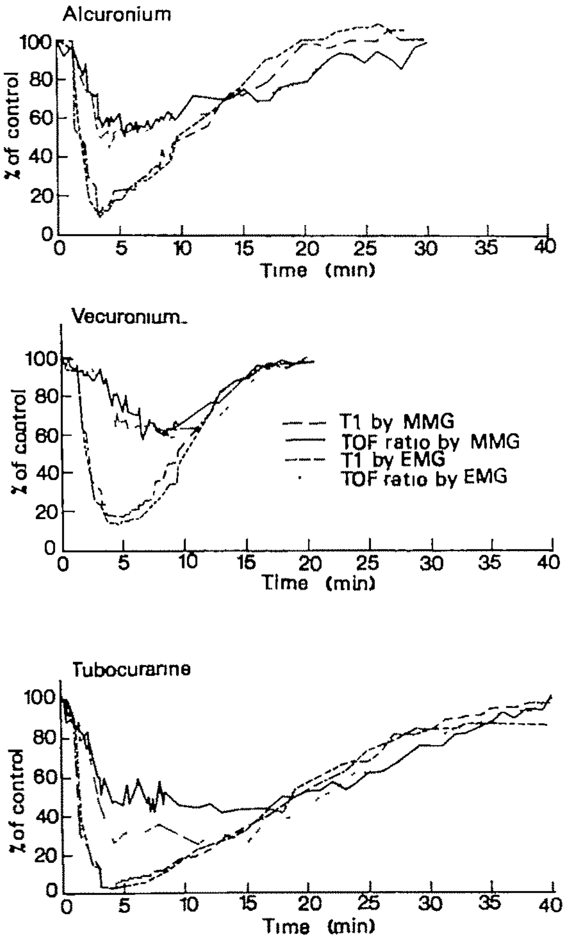

FIG. 1. Representative data from subject 4: T1 and TOF ratio recorded by MMG and EMG, plotted against time from inflation of the cuff. The three blocking drugs were tested in the same subject at 1-week intervals.

There was good correlation between MMG and EMG measurements of $T1_{rec}$ for all three drugs and of $T1_{min}$ for vecuronium ($P < 0.02$), but poor correlation in estimating $T1_{min}$ for alcuronium and tubocurarine ($P > 0.07$).

Analysis of T1 and TOF ratio responses

Figure 2 shows scattergrams of all T1 and TOF ratio values recorded by MMG and EMG for three drugs in all subjects. The line shown indicates the theoretical 1:1 relationship. The scattergrams show that there is perceptible deviation from the 1:1 relationship for alcuronium and tubocurarine which is caused by the "bias" of one

TABLE I. *Simplified summary of T1 responses from all subjects.* $T1_{min}$ *is the minimum value recorded as a percentage of the control value and* $T1_{rec}$ *the time (min) taken for T1 to recover between 25% and 75% of the control value. Results are shown for MMG and EMG recordings*

	MMG						EMG					
Subject:	1	2	3	4	5	6	1	2	3	4	5	6
$T1_{min}$ (% of control)												
Alcuronium	1	16	30	11	31	29	17	10	47	9	14	26
Tubocurarine	14	16	43	3	37	18	6	8	29	3	48	34
Vecuronium	1	1	29	18	24	39	1	9	37	14	30	46
$T1_{rec}$ (min)												
Alcuronium	12	16	9	5	13.5	9	11	17	12	5	12	7
Tubocurarine	13	24	12	13	6	14	16	25	12	9	4	13
Vecuronium	12	18	8	5	16	16	11	25	8	3	10	17

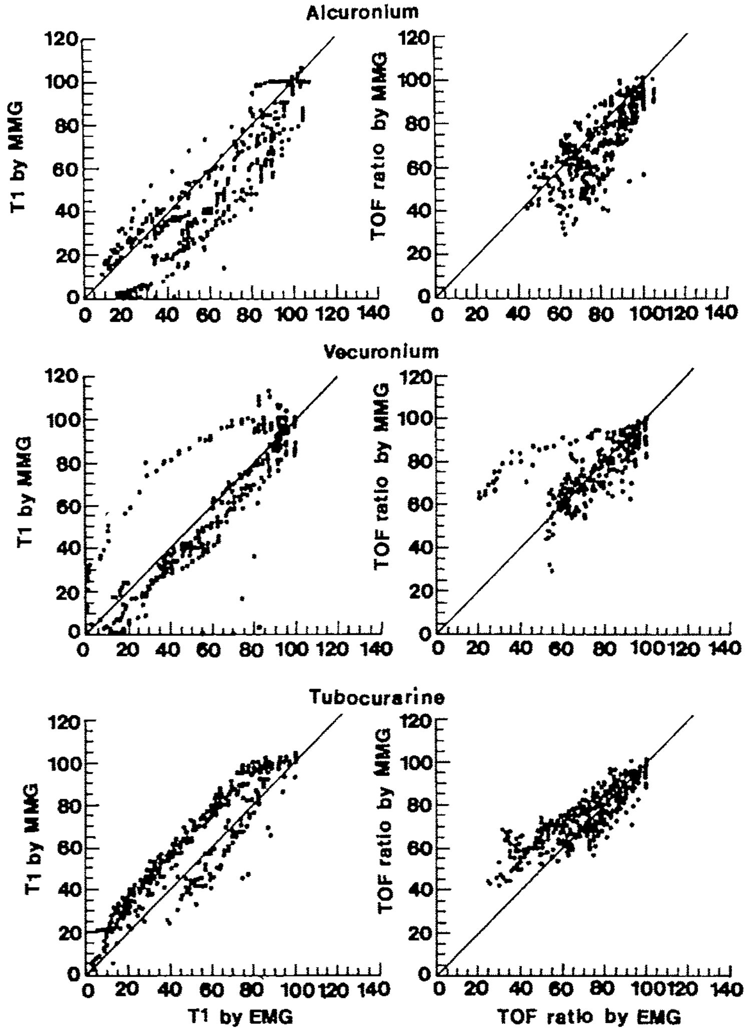

FIG. 2. Relationships between T1 by MMG and T1 by EMG, and between TOF ratio by MMG and TOF ratio by EMG from all data points. The straight lines are the theoretical 1:1 relationship. There is visible departure from this relationship in the case of alcuronium and tubocurarine.

TABLE II. *Bias between MMG and EMG measurements (MMG–EMG) of T1 and TOF ratio from all data points. There is significant bias for T1 in the case of alcuronium* (P = 0.03)

	Vecuronium		Alcuronium		Tubocurarine	
Subject	T1	TOF ratio	T1	TOF ratio	T1	TOF ratio
1	14.5	21.7	−18.9	−17.7	9.9	9.1
2	−3.9	−7.2	−11.1	−17.5	14.9	1.2
3	4.5	2.1	−1.4	1.1	0.9	3.4
4	1.0	1.7	−17.6	−11.5	−5.1	−5.7
5	−5.0	−1.5	−12.2	−5.6	14.8	4.8
6	−8.3	−7.3	1.0	0.3	13.4	7.8
Mean	0.5	1.6	−10.0	−8.5	8.1	3.4
P	0.88	0.72	0.03	0.06	0.06	0.18

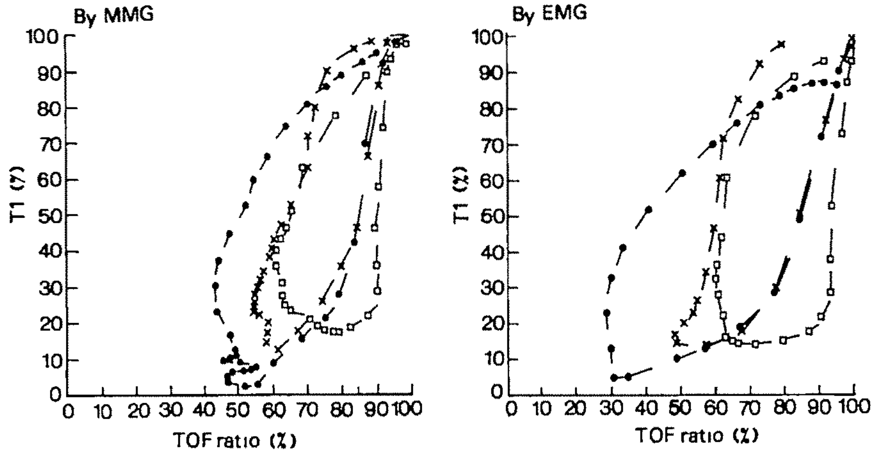

FIG. 3. Relationships between T1 and TOF ratio in subject 4. Data from figure 2 for MMG and EMG have been replotted and show a different relationship between T1 and TOF ratio depending on whether measurement is made during onset or recovery of neuromuscular block. The direction of the onset–recovery cycle is given by the symbol at the end of the broken lines: □ = vecuronium; x = alcuronium; ● = tubocurarine.

technique reading higher than the other. No overall bias is obvious for the vecuronium data, except for one line of points all of which were obtained in subject 1. Numerical analysis of the bias for all T1 and TOF ratio results in the six subjects is presented in table II. There is a significant average T1 bias in the case of alcuronium: −10.0 (SD 8.2) ($t = -2.99$, df = 5, $P = 0.03$) with 95% confidence interval (95% CI) −18.6 to −1.4. Other analyses of bias failed to achieve statistical significance, although for tubocurarine the average T1 bias of 8.1 (8.4) (95% CI −0.7 to 16.9; $t = 2.36$, df = 5, $P = 0.06$) shows a trend in the opposite direction. Only alcuronium showed an indication of average bias for TOF ratio recording (mean −8.5 (8.4) (95% CI −17.3 to 0.3; $t = -2.48$, df = 5, $P = 0.06$)), but the result again just failed to achieve significance. If the data in table II are analysed by two-way analysis of variance there is a significant difference between the average MMG–EMG T1 bias for the three drugs ($F = 5.92$, df = 2, 10, $P = 0.02$) which is demonstrated most clearly between alcuronium and tubocurarine (95% CI for the difference between the mean bias: 6.3–29.9). Analysis of variance of MMG–EMG TOF ratio values in table II shows no significant drug-related technique bias ($F = 3.29$, df = 2, 10, $P = 0.08$).

Relationship between T1 and TOF ratio

Figure 3 shows the data from figure 1 replotted to give the relationships between T1 and TOF

TABLE III. *TOF ratios at T1 = 50% of control (TOF ratio$_{50}$) for all subject–drug combinations. Paired* t *test analysis shows a significant difference in every case between values during onset (O) and recovery (R) of neuromuscular block measured by both MMG and EMG.* * *Subjects did not become paralysed to T1 = 50%; mid-point of loop taken for comparison*

	EMG			MMG		
Subject	O	R	O−R	O	R	O−R
Vecuronium						
1	88	38	50	83	64	19
2	93	60	33	84	68	16
3	92	63	29	85	58	27
4	94	63	31	90	66	24
5	92*	66	26	91	68	23
6	90	60	30	93	62	31
Mean paired diff.			33.2			23.3
SD			8.6			5.4
P			< 0.001			< 0.001
Alcuronium						
1	90	61	29	67	58	9
2	90	63	27	84	68	16
3	92*	74	18	73	56	17
4	84	60	24	85	64	21
5	91	69	22	85	71	14
6	91	67	24	80	58	22
Mean paired diff.			24			16.5
SD			3.9			4.8
P			< 0.001			< 0.001
Tubocurarine						
1	90	48	42	82	55	27
2	91	70	21	85	72	13
3	86	63	23	79*	69	10
4	84	40	44	85	50	35
5	96	50	46	86	63	23
6	94*	74	20	85	68	17
Mean paired diff.			32.7			20.8
SD			12.5			9.4
P			0.002			0.004

ratio for the three drugs studied. In each case the relationship between the two is different during onset and recovery of block, resulting in hysteresis. This feature was seen for all subject–drug combinations, recorded using MMG and EMG. To analyse the factors affecting the loop shape, values of TOF ratio at a T1 value of 50% (the TOF ratio$_{50}$ value) during onset (O) and recovery (R) of paralysis were selected from each set of curves for each subject. This provided a simple estimate of the difference in fade during these periods and was necessary because of the variable loop shapes produced by the T1 *v.* TOF ratio plots.

Complete TOF ratio$_{50}$ values for all subjects are presented in table III. In the three instances marked with an asterisk the subjects did not become paralysed to T1 = 50% and the approximate mid-point of the loop was taken as a comparison point instead. The differences between onset and recovery values of TOF ratio$_{50}$ (TOF ratio$_{50}$ (O–R)) measured by MMG and EMG were tested using the paired *t* test (table III). The onset values were found to be significantly higher than the recovery values in all subjects, with the mean difference ranging between 16.5 and 33.2 ($P < 0.005$). Two-way analysis of variance of the TOF ratio$_{50}$ (O–R) values showed considerable between-subject variability and no significant difference between any pair of drugs in contribution to the shape of the loop as determined by TOF ratio$_{50}$.

DISCUSSION

The isolated forearm technique offers a means of investigating the action of neuromuscular blocking drugs in non-anaesthetized subjects. Although introduced several years ago [10], the technique has been relatively neglected as a research tool, although a modification has been suggested for use in clinical neurophysiology [14]. In the study reported here it was used successfully in six subjects during three, weekly sessions in which train-of-four stimuli were delivered regularly for periods of up to 1 h. Simultaneous recording of MMG and EMG showed good correlation between mechanical and electrical recording of the action of adductor pollicis in assessing T1$_{\text{rec}}$ for block by alcuronium, vecuronium or tubocurarine and for T1$_{\text{min}}$ following vecuronium. There was poor agreement between the techniques in assessing T1$_{\text{min}}$ after alcuronium or tubocurarine.

Detailed analysis of all data points revealed a drug-related bias between the two recording methods for T1. We have found that EMG recorded significantly higher values than MMG during alcuronium blockade ($P = 0.03$), where the mean bias (the average value of MMG − EMG) for the six subjects was −10.0 (95% CI 18.6 to −1.4). For tubocurarine, however, the mean bias was 8.1 (95% CI −0.7 to 16.9), but the result failed to achieve significance ($P = 0.06$). The bias for alcuronium is in agreement with the finding of Harper, Bradshaw and Healy [5]. There have been a number of other studies which showed disparity between mechanical and electrical measurements of neuromuscular block, but interpretation is complicated by the different conditions of anaesthesia and test stimulations used. De Jong and Freund [15] compared tetanic tension with EMG single peak height. Following a 5-s tetanus at 40 Hz in patients anaesthetized with nitrous oxide and halothane and paralysed with suxamethonium or decamethonium, they concluded that MMG and EMG could be used interchangeably. Katz [16] found that MMG from thenar and hypothenar muscles paralysed with suxamethonium following 0.1- and 50-Hz stimuli was less than EMG. For tubocurarine the reverse applied, and the author concluded that, wherever possible, MMG and EMG should be studied independently. Epstein and Epstein [17] found wide variations between MMG and EMG from adductor pollicis in patients anaesthetized with nitrous oxide and halothane. More recently, Crul and his co-workers [9] have shown good agreement between integrated EMG and MMG from adductor pollicis stimulated with trains-of-four.

The present study has also shown that, for both MMG and EMG, there is a significant difference between the relationship of T1 and TOF ratio during onset and recovery of neuromuscular blockade—an effect which might be termed "differential fade". The results confirm, in non-anaesthetized subjects, previous clinical observations [6,7]. We were unable to demonstrate any drug-related influence on differential fade using the TOF ratio$_{50}$ method. This may be because of the relative insensitivity of the isolated forearm technique. Analysis of variance showed some between-subject variation, which questions the assumption that the subjects studied were neurophysiologically homogeneous in terms of fibre type mosaic and safety margin [18]. Muscle biopsy would have clarified this point, but was not possible in this volunteer study.

Bowman has suggested that differential fade may be caused by different affinities of non-depolarizing neuromuscular blocking drugs for pre- and post-junctional receptors at the neuromuscular junction [19]. Williams and his co-workers [6] showed that, during onset of paralysis, pancuronium produced the least and gallamine the most fade at 50% reduction in T1. It has been suggested [Norman, personal communication, 1987] that the newer generation of blockers may show more differential fade than the old. We were unable to show this effect between vecuronium and tubocurarine.

The findings presented here have a number of clinical implications. Care should be taken in extrapolation between MMG and EMG measurement of muscle activity. The relationship between the two techniques has been shown to be influenced by the nature of the blocking agent. The existence of differential fade implies that relationships between T1 and TOF ratio derived during recovery from block should not be used to predict values of T1 during onset.

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Br. J. Anaesth. (1989), **62**, 287–289

EFFECTS OF PIPECURONIUM AND PANCURONIUM ON THE ISOLATED RABBIT HEART

R. K. DEAM AND N. SONI

SUMMARY

We have studied the effects of pipecuronium and pancuronium on myocardial contractility and heart rate in two different animal preparations. Pipecuronium and pancuronium produced no change in isometric contraction of rabbit atria. The chronotropic effects of pipecuronium, pancuronium and vecuronium were investigated using acetylcholine as an agonist in isolated perfused rabbit heart. Pancuronium but not pipecuronium or vecuronium, produced a significant degree of antagonism to the bradycardia produced by acetylcholine.

Pipecuronium bromide is a new long acting neuromuscluar blocking drug reportedly devoid of cardiovascular side effects. It is a steroidal molecule similar in structure to pancuronium and has a potency 20% greater [1]. Its duration of action is 1.2–2.1 times longer than that of pancuronium [2]. Clinical studies suggest that this agent has no significant cardiovascular effects [3, 4], although there have been occasional reports of mild bradycardia [5, 6].

The present study was undertaken to examine the *in vitro* inotropic and chronotropic effects of pipecuronium using isolated rabbit heart preparations.

MATERIALS AND METHODS

Investigation 1

The inotropic effects of pipecuronium were studied using isolated paced left atria of rabbits. Rabbits weighing 2–3 kg were stunned by a blow on the back of the head. The heart was excised and the left atrium dissected out and suspended in a tissue bath containing Ringer–Locke solution, aerated vigorously with 100% oxygen, and maintained at a temperature of 37 °C and constant pH.

The atrium was attached to a platinum hook electrode and stimulated at a rate of 3 Hz using a square wave pulse generator at supramaximal voltage. The specimen was preloaded to a tension of 5 g. Changes in isometric tension were measured using a force displacement transducer (Grass FT03), and recorded on a Brush Clevite recorder. Each preparation was allowed to equilibrate and stabilize for 30 min before each study. Incremental concentrations of either pancuronium or pipecuronium were introduced into the bath (concentration range 4–20 μg ml^{-1}) and measurements of force of contraction were obtained at each concentration. These concentrations are similar to those used in other studies [7, 8]. The experiment was repeated with the other drug after re-establishing control conditions.

Results were expressed as the percentage change in the force of contraction from that obtained during a drug-free control period [7].

Investigation 2

In this study a modified Langendorff preparation was used. Isolated hearts of healthy rabbits were excised and perfused at a constant rate through the cut end of the aorta. The perfusate comprised oxygenated Ringer–Locke solution maintained at 37 °C and constant pH. Spontaneous ventricular contractions were measured using a Walton–Brodie strain gauge transducer stitched to the left ventricle. Each preparation was allowed to equilibrate and stabilize for 20 min with Ringer–Locke perfusate. A bolus of acetylcholine was injected into the perfusate, resulting in a reproducible change in heart rate. In a preliminary study acetylcholine 1 μg produced

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consistently a reduction in heart rate of approximately 30 %. This was the dose used by Baden [9] with similar results.

Following the equilibration period, a control injection of acetylcholine 1 µg was made close to the perfused heart and the resulting bradycardia recorded. Using random sequence, vecuronium 2.5 mg litre^{-1} or pancuronium 3 mg litre^{-1} or pipecuronium 2 mg litre^{-1} was added to the Ringer–Locke solution. These are assumed to be equipotent concentrations and thought to represent the peak plasma concentration that could be found in man, after a normal intubating dose of the drug [10], and are consistent with concentrations used by other workers [9, 11]. The solutions were perfused for 20 min before injection of acetylcholine 1 µg and the resulting bradycardia was recorded. This was repeated for the remaining two drugs after a wash-out period with Ringer–Locke solution. Finally, a further test dose of acetylcholine 1 µg was administered while the specimen was perfused with Ringer–Locke solution to act as a final control. If the final control was not comparable to the preliminary control, the results were disregarded.

RESULTS

Investigation 1

No statistical difference was found between the forces of contraction in paced rabbit atria produced by pipecuronium or pancuronium in the doses tested (table I).

Investigation 2

The 1-µg dose of acetylcholine produced a similar response in hearts perfused with Ringer–Locke, vercuronium and pipecuronium perfusates. However, with pancuronium perfusate, the change in heart rate was consistently less. Using the Wilcoxon Rank paired test no significant difference was found between the control Ringer–Locke perfusates, vecuronium or pipecuronium, but all three were significantly different from pancuronium perfusate (fig. 1).

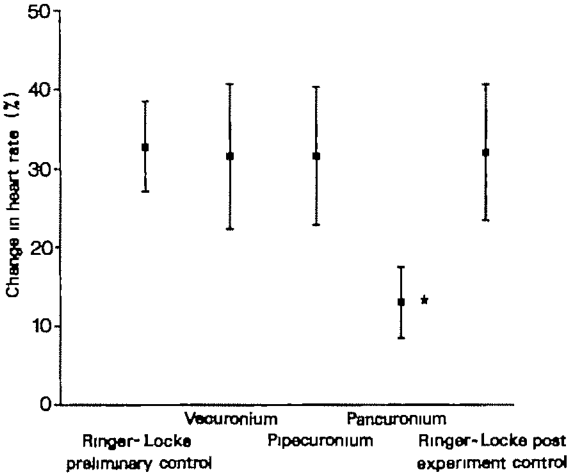

FIG. 1. Percent change in heart rate after acetylcholine 1 µg in the five different perfusates (means of eight results). $^{*}P < 0.05$.

TABLE I. *Percentage change (SD) in the force of contraction of the right atrium, with pancuronium and pipecuronium, and the probability value of the differences between them (using the Wilcoxon Rank paired test)*

Dose of drug (µg ml^{-1})	Pancuronium ($n = 10$)	Pipecuronium ($n = 10$)	P
4	1 (2.2)	2.9 (3.8)	0.2500
8	2.2 (2.9)	0.7 (2.2)	0.6250
12	4 (4.8)	1.5 (3.2)	0.4375
16	1.9 (2.6)	3.1 (3.7)	0.6250
20	3.5 (7.2)	3.9 (3.4)	1.0000
P (difference between 4 µg ml^{-1} and 20 µg ml^{-1}	0.5000	0.1000	

DISCUSSION

There are several clinical studies which have suggested that pipecuronium is similar in duration of action to pancuronium but does not possess cardiovascular side effects [1, 3, 4]. We found no statistical difference in the force of contraction of paced rabbit atria in the concentration range described, for either pipecuronium or pancuronium.

Our experimental model has been used previously to assess the inotropic effect of neuromuscular blocking drugs. Duke, Fung and Gartner [7] reported that pancuronium in concentrations from 10^{-5} to 10^{-2} g litre^{-1} did not alter the force of contraction in isolated rabbit atrial strips and this is consistent with the findings in this study. However, with other experimental models changes in contractility have been observed with neuromuscular blockers. Iwatsuki and colleagues [8] reported that pancuronium increased the force of contraction in the ventricular muscle of healthy dogs when administered in concentrations of

$2.5\text{–}30 \times 10^{-3}$ g litre^{-1}. The discrepancy between the findings in that model and in the study described here, may reflect differences in experimental conditions or species variation.

In the second investigation, the perfusate concentrations of the three myoneural blockers were comparable to those used in previous studies [9, 11]. Vecuronium was included in this study as a drug known to have no chronotropic effects. Using the control perfusate, acetylcholine caused a reproducible degree of bradycardia. The presence of vecuronium or pipecuronium did not cause a significant change in the bradycardia induced by acetylcholine. However, when the pancuronium perfusate was used there was a significantly smaller change in heart rate in response to the same dose of acetylcholine. These data are consistent with those of Goat and Feldman [11]. In their study a similar model was used and pancuronium perfusate 1 mg litre^{-1} produced partial antagonism to the acetylcholine boluses. With a concentration of 2 mg litre^{-1}, the antagonism was complete. In the study carried out by Baden [9], pancuronium perfusate 2 mg litre^{-1} resulted in a 20% decrease in heart rate following acetylcholine 1 μg injected as a bolus close to the heart. In the present study, pancuronium 3 mg litre^{-1} in the perfusate was used, and this resulted in a 13% decrease in heart rate following acetylcholine 1 μg. Our results are therefore consistent with those reported previously.

In conclusion, the clinical reports that pipecuronium has minimal cardiovascular side effects are supported by the findings of this *in vitro* study.

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Br. J. Anaesth. (1989), **62**, 290–296

CLOSED-LOOP FEEDBACK CONTROL OF PROPOFOL ANAESTHESIA BY QUANTITATIVE EEG ANALYSIS IN HUMANS

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SUMMARY

Propofol was administered for 2 h to 11 volunteers by an adaptive feedback control algorithm based on quantitative EEG analysis. Median EEG frequency served as the control variable. The range 2–3 Hz was chosen as the target range of control. During the feedback period, volunteers did not respond to commands and eyelash reflex was abolished. An average median frequency of 2.5 (SD 0.3) Hz was obtained by administering propofol 1452 (262) mg within 2 h. Time to recovery was 17.9 (8.0) min. Compared with a study with methohexitone using the same approach, the relative potency of propofol was 0.72. The mean recovery time was less than half that observed after methohexitone.

The electroencephalogram (EEG) has been used as a measure of drug action of anaesthetic compounds on the brain [1, 2]. More recent investigations include spectral EEG values to establish pharmacokinetic–pharmacodynamic models describing the drug input–effect relationship.

If the EEG correlates well with common clinical signs of depth of anaesthesia it might be used for control of anaesthesia. Median frequency of the EEG power spectrum (50% quantile) decreases as depth of anaesthesia increases. For etomidate [3], methohexitone [4] and isoflurane in nitrous oxide [5], median EEG frequencies less than 5 Hz were associated with unconsciousness as defined by non-responsiveness to verbal commands.

Appropriate rate control of drug delivery is a prerequisite to induce and maintain anaesthesia. Programmed schemes of drug administration need an adjustment for the individual subject and the varying nociceptive stimuli during surgery. Closed-loop feedback control methods [6, 7] compare the set-point of the control variable with the value actually measured to modify rate of drug delivery. When applied to a pharmacological model, this comparison is used not only to correct dosing but also to update and individualize the model parameters. This method is commonly referred to as model based, adaptive feedback control. It has been applied recently to the control of methohexitone anaesthesia in volunteers [4].

In the present study, we have examined the applicability of model based, adaptive feedback control of propofol by quantitative EEG analysis in volunteers and compared this with the previous study of methohexitone.

SUBJECTS AND METHODS

Eleven volunteers (24–31 yr, 54–87 kg, 162–197 cm) were studied after their informed written consent and institutional approval were obtained. After placing a cannula in a forearm vein and installing clinical monitoring, the baseline EEG was recorded. Four EEG leads (C_z–F_i; C_z–O_i i = 1,2) were amplified (Mingograph Junior, Siemens) and recorded on magnetic tape (PR 2200, Ampex). The C_z–O_i i = 1,2 lead, having the lower impedance, was used for deriving the feedback signal.

Before induction of anaesthesia, the volunteers listened to music via earphones to smooth induction of anaesthesia and to lessen the awareness of the start of infusion. After recording the baseline

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EEG, feedback control of propofol was instituted and maintained for 2 h. During the feedback control period, volunteers were exposed randomly to stimulation consisting of six types of stimuli: acoustic sensations, verbal commands, cold stimuli, pin pricks, and testing of eyelash and corneal reflexes, approximately every 1.5 min. Blood samples from a capillary in the ear lobe were taken every 20 min for measurement of gas tensions.

EEG analysis

The filter settings of the EEG amplifier were 0.3 s and 70 Hz. Before A–D conversion, the signal was analog filtered between 0.5 and 32 Hz, segmented into epochs of 8.192 s, and digitized at a rate of 125 Hz with 12-bit A–D resolution. For each epoch, the power spectrum between 0.5 and 32 Hz was calculated using common Fast-Fourier-Transformation (FFT) algorithms from which the median EEG frequency (50 % quantile) of the power spectrum was derived. In addition, off-line analysis included calculation of fractional power in the frequency bands 0.5–2 Hz, > 2–5 Hz, > 5–8 Hz, > 8–13 Hz, > 13–32 Hz, and mean amplitude. For data smoothing, a moving average of nine epochs was performed.

Administration device and algorithm

Two infusion pumps (IP 4, Vickers) were attached in parallel to the computer (Eurocom 3, Eltec) by bypassing the digitial switches electronically. The maximum rate of propofol administration was thus confined to 33.3 mg min^{-1}. The start of the automatic feedback control was preceded by a 4-min infusion of propofol at maximum rate. The subsequent rates of propofol infusion were determined on the basis of the feedback signal and the pharmacokinetic–dynamic model used for propofol. According to previous work [8] a linear two-compartment model was used to describe the drug input–concentration relationship. The relation between concentration C and slowing of median EEG frequency E was modelled by the sigmoid function:

$$E = E_0 - E_{\max} \frac{C^\gamma}{C^\gamma + C^\gamma_0}$$

where E_0 represents the baseline median EEG frequency, $E_0 - E_{\max}$ its maximum decrease, C_0 the concentration at half maximum effect and γ the steepness of the concentration–effect relationship.

As initial values, a baseline median EEG frequency of 9 Hz and a maximum decrease to 1 Hz were chosen. Concentration at half maximum effect was assumed to be 2.5 μg ml^{-1} and γ was set to 2.5, according to estimations from previously performed open-loop studies in volunteers. The interval of 2–3 Hz of median EEG frequency was used as the desired degree of EEG slowing.

A first update of the model parameters was performed after the initial period of 4 min. During the subsequent period of time, the following algorithm [4] was used: if median EEG frequency was within the range 2–3 Hz, propofol was administered by a B.E.T. (Bolus, Elimination, Transfer algorithm) infusion scheme [9, 10] aiming at maintaining the current predicted concentration. If median EEG frequency was outside this range, the difference between the measured and predicted values served to adapt the

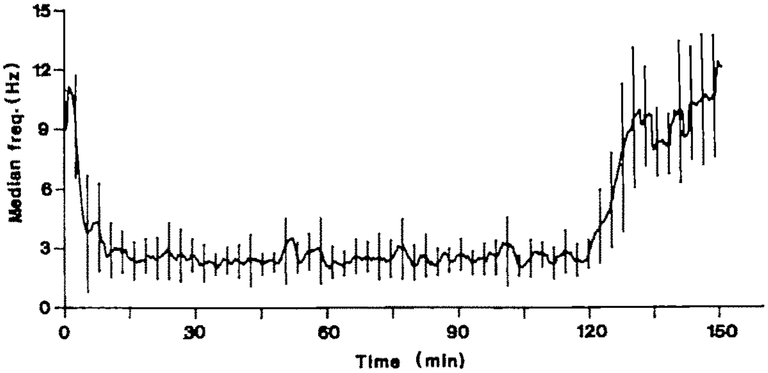

FIG. 1. Mean (SD) time course of median EEG frequency during feedback control of propofol anaesthesia aiming at a median frequency in the range 2–3 Hz.

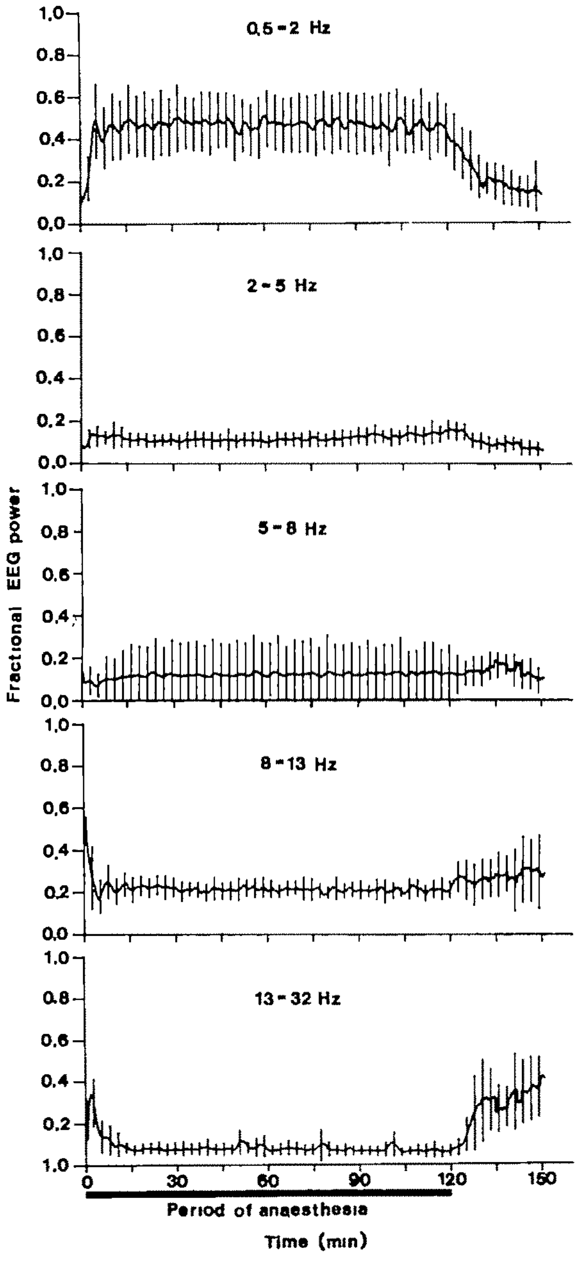

FIG. 2. Mean (SD) time course of fractional EEG power during feedback control of propofol anaesthesia aiming at a median frequency in the range 2–3 Hz.

model parameters (Appendix). On the basis of the updated parameters, a new infusion scheme was calculated for achieving and maintaining a concentration inducing a median EEG frequency of 2.5 Hz.

For hypothesis testing, the Wilcoxon and the

TABLE I. *EEG parameter values of 11 volunteers participating in closed-loop feedback control of propofol anaesthesia at baseline (B), during feedback control (F) and at recovery (R, orientation with respect to time and location), and time to recovery (T)*

	Fractional EEG power															Median (Hz)			Amplitude (µV)			Time (min)
	0.5–2 Hz			> 2–5 Hz			> 5–8 Hz			> 8–13 Hz			> 13–32 Hz									
Volunteer	B	F	R	B	F	R	B	F	R	B	F	R	B	F	R	B	F	R	B	F	R	T
1	13.2	45.9	7.8	4.6	8.9	7.6	8.4	9.3	9.6	47.3	22.4	28.9	26.4	13.4	46.1	10.2	2.8	11.2	12.4	23.7	12.3	14.7
2	3.0	47.4	5.6	3.2	16.9	6.1	11.3	8.6	21.8	83.6	21.6	44.6	6.4	5.4	21.9	10.3	2.2	9.3	15.3	22.0	19.8	16.2
3	16.6	46.3	8.8	14.2	16.0	11.9	7.4	10.1	10.4	50.0	23.2	44.6	11.8	4.3	53.1	10.7	2.7	13.6	9.3	24.5	12.6	38.8
4	11.9	52.1	17.9	11.7	12.0	8.4	10.8	6.2	2.9	50.9	19.8	6.7	14.6	9.8	64.0	10.8	2.3	15.8	7.3	19.0	9.8	19.8
5	23.0	53.7	12.6	15.4	10.2	6.9	3.2	7.2	6.8	27.3	20.8	13.3	24.7	7.9	60.3	9.4	2.3	14.8	19.6	19.6	10.2	12.2
6	4.2	44.6	18.4	4.9	14.1	8.9	4.2	8.9	12.9	70.8	24.8	24.5	10.9	7.4	35.3	10.6	3.2	10.3	12.8	12.3	12.5	11.0
7	19.8	52.6	8.1	12.2	12.3	6.2	16.7	8.3	11.7	36.8	21.8	39.8	14.4	4.9	33.7	8.2	2.6	10.6	5.5	17.7	12.1	24.0
8	13.8	52.2	24.0	5.9	13.9	6.7	7.5	5.9	11.4	52.9	17.7	25.7	19.9	10.1	32.2	9.9	2.6	9.3	14.5	16.9	12.9	11.4
9	10.7	53.4	21.3	3.0	10.2	7.2	3.4	7.3	16.1	78.6	21.4	28.4	4.3	7.6	26.9	10.5	2.4	8.7	13.7	16.0	13.5	13.0
10	9.9	51.2	12.1	6.0	12.4	10.2	15.0	6.9	20.5	59.3	19.1	18.5	9.8	10.2	38.7	9.4	2.4	9.7	11.0	13.0	11.5	14.7
11	9.0	52.2	17.9	3.8	10.5	9.5	5.6	7.5	20.8	77.6	21.1	24.9	4.3	8.5	26.9	9.3	2.4	8.0	13.6	12.2	11.6	19.6
Mean	12.3	50.1	14.0	7.7	12.9	8.1	8.5	7.8	13.2	57.7	21.2	24.6	13.4	8.1	39.9	9.9	2.5	11.0	12.3	17.9	12.6	17.8
SD	6.0	3.4	6.2	4.7	2.5	1.8	4.5	1.3	6.1	18.1	1.9	11.1	7.6	2.6	14.1	0.8	0.3	2.6	3.9	4.4	2.6	8.0

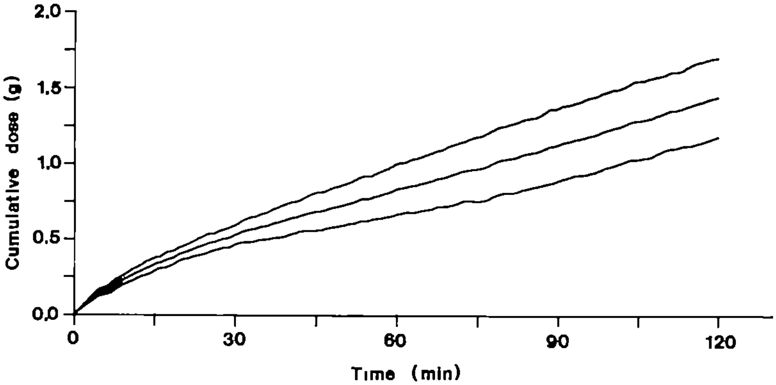

FIG. 3. Mean cumulative dose of propofol required to maintain median EEG frequency in the range 2–3 Hz.

Mann–Whitney *U* tests were used. The non-parametric Levene test was used to compare the variance of different distributions.

RESULTS

During induction of anaesthesia, none of the volunteers showed signs of excitation. All were unresponsive to verbal commands during the feedback period. Eyelash reflex was always absent and, in general, corneal reflex was abolished.

Mean time to achieve the desired range of control was 10.4 (SD 4.6) min, during which propofol 256 (91) mg was administered. The average time course of median EEG frequency for the 11 volunteers is shown in figure 1. The distribution of all median EEG frequencies during the feedback period showed a mean of 2.53 Hz and a median of 2.45 Hz. The inter-quartile range was 1.5–3.6 Hz. The decrease of median EEG frequency was caused mainly by an increase of low frequency activity in the range 0.5–2 Hz (fig. 2). This activity increased from 11 % to approximately 50 % of total EEG activity at anaesthetic states associated with non-responsiveness to verbal commands.

The EEG values at baseline (B), during the feedback control period (F) and at recovery (R; orientation with respect to time and location), in addition to time to recovery (T) are shown in table I. Comparison of the EEG obtained during baseline and feedback showed a significant difference ($P < 0.05$) for all values except fractional power between 5–8 Hz and 13–32 Hz. Comparison of the baseline period with recovery showed no significant difference except for fractional power in bands 8–13 Hz and 13–32 Hz. It appears from table I that the interindividual variability of EEG values decreases from baseline to anaesthetic values. Testing for different variabilities (Levene test, $P < 0.05$) demonstrated significantly smaller variability during anaesthesia than during baseline, except for amplitude and fractional power between 0.5 and 2 Hz. The average amount of propofol required during the 2 h procedure was 1452 (262) mg. The cumulative amount of propofol delivered is shown in figure 3. The terminal slope of the cumulative dose curve is 10.2 (0.9) mg min^{-1}.

Comparison with methohexitone

The 11 volunteers in this study did not differ significantly with respect to age, body weight and height from the group of 11 volunteers studied in a previous feedback control investigation with methohexitone [4]; nor did each group differ with respect to baseline EEG parameters. However, a significant difference was observed in the EEG frequency distribution during anaesthesia, while median EEG frequency and amplitude did not differ between the groups. Compared with methohexitone, propofol increased activity in the frequency bands 0.5–2 Hz, 8–13 Hz and 13–32 Hz and decreased activity in the frequency bands 2–5 Hz and 5–8 Hz. The ratio of cumulative doses of propofol required in this study and of methohexitone in the previous study is given in figure 4. The average ratio of methohexitone to propofol dose to maintain a median EEG frequency of 2.5 Hz was 0.72. The recovery time from stopping the infusion to orientation with respect to time and location was both more rapid and more

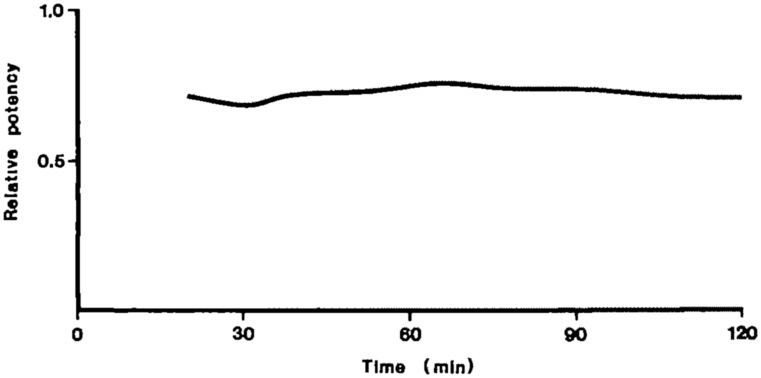

FIG. 4. Relative potency of propofol with respect to methohexitone, obtained from mean cumulative dose curves required to maintain median EEG frequency in the range 2–3 Hz in 11 volunteers treated with propofol and methohexitone [4].

predictable with propofol than with methohexitone (17.9 (8.0) min and 40.2 (16.9) min, respectively).

DISCUSSION

Models can be used to derive dose regimens to induce and maintain a desired anaesthetic effect in the average patient. However, programmed drug administration may need some means of adjustment when applied to a specific subject under varying conditions of surgery. Population pharmacokinetics [11, 12] may identify the influence of various anthropometric and physiological variables on the individual disposition of drugs. However, if the pharmacodynamic response can be measured continuously, it is a reasonable approach to use this information for adjustment of drug delivery.

Engineering sciences have developed a number of methods for the automatic control of processes. In this paper, we used model based, adaptive feedback control for administration of propofol. Using established pharmacokinetic–dynamic models, one can calculate programmed schemes of drug administration as a first approximation to the individual drug requirement. The controller has to identify subsequently only individual corrections to the suggested administration scheme. The adaptive feature of the controller was designed to compensate for different co-medications and time-varying events in surgical patients.

Our results show that, under the conditions of frequent random stimulation, the controller succeeds in maintaining anaesthesia (defined by nonresponsiveness to verbal commands) by propofol administration. Given the target range of 2–3 Hz for median EEG frequency, the average median frequency of 2.53 Hz obtained shows that the controller works accurately, as has previously been shown also with methohexitone [4]. The precision in the present study was less than in the case of methohexitone. The interquartile range for the distribution of median EEG frequency lay between 1.5 Hz and 3.6 Hz for the propofol study and between 2 Hz and 3 Hz for methohexitone. However, our clinical impression did not indicate a less stable time course of anaesthesia, as judged by responsiveness to the various stimuli, in the case of propofol than in the case of methohexitone.

The residual α-activity was about 21 % and β-activity about 9 % of total EEG activity during feedback control (table I), compared with 16 % of residual α-activity and 6 % of β-activity in methohexitone anaesthesia. A more pronounced bimodal shape of the EEG power spectrum could account partially for the wider scatter of median EEG frequency during propofol anaesthesia. Other reasons (e.g. a steeper concentration–response curve, or hysteresis between dosing and effect) require more detailed investigation of the EEG of propofol and its relationship to dosing. When comparing the EEG power distribution during baseline and recovery, we observed a significant decrease of α-activity and increase of β-activity, while the comparison of the baseline values with the anaesthesia period showed no significant changes in θ-activity (5–8 Hz) and β-activity. These findings suggest that the anaesthetic state induced by propofol is accompanied by a shift from α-activity to below 5 Hz, while residual propofol effects, which might include states of light sedation, are characterized by β-activation.

The relative potency of propofol, compared with methohexitone, was 0.72. This ratio calculated from cumulative dose requirements after the 20th min of methohexitone and propofol administration, after which time all volunteers of both groups had reached the desired range of control. This ratio may not necessarily apply to bolus doses. The average amount of methohexitone necessary to achieve the range 2–3 Hz of median EEG frequency was 192 (102) mg within a time of 9.6 (5.2) min, compared with propofol 253 (91) mg given within 10.4 (8.0) min, indicating, for that shorter period of time, a potency ratio of 0.76. Relative potencies expressed in terms of drug requirements are influenced by different quantities when estimated from bolus dose or from drug requirements at steady-state. In addition to concentration at the biophase, initial volume of distribution and its equilibration with the active site play an important role after bolus administration, while clearance is a factor to be considered when comparing drug requirements at steady-state. The relative potency of propofol and the average rate of infusion of propofol agree reasonably well with findings of Mackenzie and Grant [13]. To maintain general anaesthesia during regional anaesthesia in non-premedicated patients scheduled to undergo surgery of the lower limbs, they found a rate of infusion of 0.13 mg kg^{-1} min^{-1} for propofol and 0.089 mg kg^{-1} min^{-1} for methohexitone, corresponding to a rate of 9.1 mg min^{-1} of propofol for a 70-kg patient and to a relative potency of 0.68. However, this study gave no data on recovery times for propofol and methohexitone. Another study [14] of premedicated patients given either propofol or methohexitone to maintain general anaesthesia during surgery with regional blockade found maintenance doses of 0.103 mg kg^{-1} min^{-1} of propofol and 0.104 mg kg^{-1} min^{-1} of methohexitone, indicating a relative potency of 1. In agreement with the results of our study, the recovery time after propofol anaesthesia was less than 50% of the recovery time after methohexitone anaesthesia. The seemingly conflicting results of these studies emphasize the need for objective methods in defining drug requirement for maintaining anaesthesia. The feedback control approach of anaesthetic drug delivery is such a method, suited for both pharmacological research and therapy.

Feedback control methods in the clinical situation require a fail-safe system. The most important complication, when using the EEG, is sensor failure as a result of high frequency electrical interference. We believe that the pharmacokinetic–dynamic model used in constructing the controller could be a reasonable solution to this problem. In the case of a recognized sensor failure, the system can switch to the open-loop mode, during which the rate of drug administration is calculated on the basis of the updated model.

APPENDIX

ADAPTATION ALGORITHM

The pharmacokinetic–dynamic model used consists of two formulae: a relation between drug input function $I(t)$ and drug concentration $C(t)$:

$$C(t) = \int_0^t dt' G(t-t') I(t') \tag{1}$$

and a relation between concentration $C(t)$ and effect $E(t)$.

$$E = E_0 - E_{max} \frac{C^\gamma}{C^\gamma + C_0^\gamma} \tag{2}$$

whereby the function $G(t)$ is given by the blood concentration after a bolus of unit dose, that is.

$$G(t) = A \exp(-\alpha t) + B \exp(-\beta t)$$

Inserting equation (1) into equation (2) immediately relates drug dosing $I(t)$ to effect, and eliminates one parameter of the set of eight (A, α, B, β, E_0, E_1, C_0, γ) because it depends only on the ratios A/C_0 and B/C_0 as a result of the scale invariance of equation (2) under the transformation $(C, C_0) \rightarrow (\lambda C, \lambda C_0)$.

Given any desired effect E, equation (2) may be inverted to give the desired concentration and equation (1) may subsequently be inverted to give the necessary drug input function.

A full adaptation algorithm requires an estimation of all seven parameters. This can be achieved only if the duration of the investigation is long enough to determine the largest half-life and the signal output is sensitive to all parameters, which requires in general a wide variation of concentration and effect. The present study has had the aim of maintaining the signal within a predefined band. Therefore we confined the parameters to be adjusted to A and B. Such a choice allows adjustment of both initial volume of distribution (a major determinant of the subject's response immediately after a bolus dose) and clearance (which has an important impact on the subject's response to steady-state infusion).

The effect E may be regarded as a function of A and B and the drug input $I(t)$:

$$E = E(A, B, I(t))$$

Denoting by $A+\delta A$ and $B+\delta B$ the true hybrid constants for an individual subject, the difference between measured and predicted effect (ΔE) can be expanded in a Taylor series, as follows:

$$E = E(A+\delta A, B+\delta B, I(t)) - E(A, B, I(t)) = (\partial E/\partial A)\delta A + (\partial E/\partial B)\delta B + \dots \tag{3}$$

In conjunction with the condition to minimize the expression $\delta A^2 + \delta B^2$, equation (3) was used to solve for δA and δB. From the updated values, new microconstants were calculated that served to correct the drug input function.

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EFFECTS OF HALOTHANE ON SOMATOSENSORY EVOKED POTENTIALS RECORDED IN THE EXTRADURAL SPACE

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SUMMARY

We studied the effects of supplementing anaesthesia with halothane (up to 1.5%, inspired) on the somatosensory evoked potential recorded in the extradural space of six patients before corrective surgery for idiopathic adolescent scoliosis. A further six patients in whom anaesthesia was supplemented with thiopentone acted as a control group. Halothane 1.5% resulted in a significant decrease in overall amplitude ($P <$ 0.05) from the left leg only. Halothane had no significant effect on overall amplitude, first peak amplitude, second peak amplitude and first peak latency. We conclude that halothane is unlikely to alter the interpretation of somatosensory evoked potentials recorded extradurally during scoliosis surgery. A possible unilateral effect of halothane on the concave side in idiopathic adolescent scoliosis needs further investigation.

Evoked potentials provide information on the continuity of a nervous pathway. Grundy [1] has reviewed the intraoperative monitoring of evoked potentials and she suggested that their interpretation may need to take into account the effects of anaesthetic drugs. This is important particularly for somatosensory evoked potentials (SEP) recorded cortically [2].

In 1983 Jones and colleagues [3] described the recording of SEP in the extradural space during corrective surgery for scoliosis. Signals recorded by this method are subject to less electrical interference, are of large amplitude, are comparatively easy to interpret and provide a direct indication of spinal cord function. Attenuation of the SEP measured extradurally is seen in association with cord ischaemia, compression or distraction [3–5]. Anaesthetic agents are considered to have less effect on the SEP recorded extradurally than on its counterpart measured from the scalp [3]. However, there are few data in man to support this contention. Therefore, in the present study we have examined the effects of increasing concentrations of halothane on the SEP recorded in the extradural space.

PATIENTS AND METHODS

We studied 12 patients (11 female, 1 male; mean age 17 yr) admitted to the Royal National Orthopaedic Hospital for corrective surgery for idiopathic adolescent scoliosis. All patients had a scoliosis which was concave to the left and with a Cobb angle between 30° and 70° as assessed by plain erect x-rays. The degree of scoliosis was similar in both groups. The study was approved by the Hospital Ethics Committee and written, informed consent was obtained from the patients, or their parents, as appropriate.

All patients were premedicated with papaveretum 0.3 mg kg^{-1} and hyoscine 0.006 mg kg^{-1} i.m. 1 h before induction of anaesthesia with thiopentone 4 mg kg^{-1}. Intubation of the trachea was facilitated with suxamethonium 1 mg kg^{-1}. The lungs were ventilated with 70% nitrous oxide in oxygen and a radial artery was cannulated for the measurement of arterial pressure. The patients were placed in a prone position on a

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Montreal mattress and the extradural space located at the C7–T1 space using a 16-gauge Tuohy needle and the "hanging-drop" technique. A 3 French-gauge cardiac pacing wire (S-pace, Medical Ltd) was passed through the needle cephalad and connected to the preamplifier of a Medelec MS 91 electromyograph recorder.

The right and left posterior tibial nerves were stimulated alternately via skin surface electrodes using a square-wave impulse of 0.2 ms duration at an intensity of 150 µV. The stimulation frequency was 20 s^{-1} and 1000 responses were averaged with a resolution of 0.033 ms. The filters were set at 200 Hz to 2 KHz. Increments of thiopentone 50 mg were administered i.v. if required during instrumentation. A minimum of two baseline recordings were made in all patients who were assigned randomly either to receive halothane ($n = 6$) or to enter a control group ($n = 6$).

In the halothane group, the patients underwent artificial ventilation with increasing concentrations of halothane in increments of 0.5% every 15 min until the end-tidal concentration equalled the inspired concentration (Datex, halothane meter). Two SEP were recorded from the extradural space after equilibration at each halothane concentration: 0.5%, 1.0% and 1.5%. In the control group of patients thiopentone was administered in increments of 50 mg i.v. when indicated clinically and two SEP were recorded at equivalent 15-min intervals. Mean arterial pressure was measured also at each time point. Ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 3.5–4.5% and rectal temperature remained greater than 35 °C. At the end of the investigation the patient was taken into theatre and surgery commenced. The extradural electrode was then used to monitor SEP during the corrective surgery.

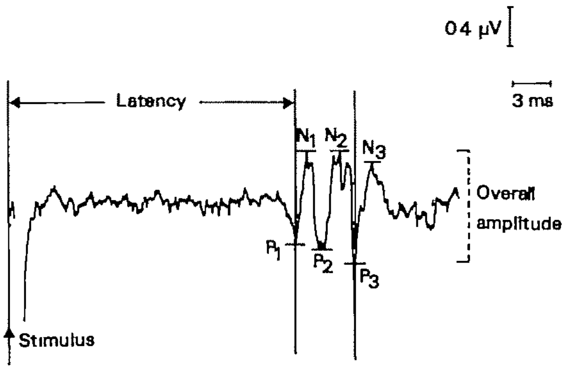

FIG. 1. Typical somatosensory evoked potential recorded in the extradural space showing first peak (P_1N_1), second peak (P_2N_2), third peak (P_3N_3) and overall amplitudes.

A typical SEP recorded in the extradural space is shown in figure 1. The potentials were analysed for overall amplitude (maximum amplitude between most positive wave and most negative wave), first peak-to-peak amplitude (P_1N_1), second peak to peak amplitude (P_2N_2) and first peak latency. The shapes of the peaks derived from stimulation of the right and left leg remained the same throughout the study and this was used to indicate that the position of the recording electrode had not altered.

The results are presented as medians and ranges. Because of the small number of patients studied and the skewed distribution of the data, statistical evaluation was undertaken using non-parametric tests. The Wilcoxon signed rank test, Mann–Whitney *U* test, and Kendall's rank correlation coefficient (τ) were used as appropriate.

TABLE I. *Median (range) overall amplitude of SEP (µV) in patients receiving halothane or thiopentone. * Significant difference from baseline* ($P < 0.05$)

	Halothane ($n = 6$)		Control ($n = 6$)	
	R leg	L leg	R leg	L leg
Baseline	0.84 (0.56–1.14)	0.65 (0.46–1.16)	1.10 (0.73–1.59)	1.20 (0.69–2.14)
15 min (0.5% halothane)	0.81 (0.56–1.20)	0.58 (0.44–1.31)	0.98 (0.82–1.78)	1.18 (0.81–2.06)
30 min (1% halothane)	0.69 (0.42–1.16)	0.52 (0.32–1.16)	1.18 (0.93–1.82)	1.22 (0.81–2.16)
45 min (1.5% halothane)	0.73 (0.50–1.00)	0.48* (0.32–1.14)	1.09 (0.83–1.65)	1.20 (0.69–1.75)

TABLE II. *Median (range) first peak amplitude (μV) in patients receiving halothane or thiopentone*

	Halothane ($n = 6$)		Control ($n = 6$)	
	R leg	L leg	R leg	L leg
Baseline	0.68 (0.31–0.92)	0.46 (0.33–1.02)	0.76 (0.51–1.56)	0.99 (0.25–1.59)
15 min (0.5 % halothane)	0.72 (0.28–0.96)	0.42 (0.30–0.96)	0.77 (0.49–1.78)	0.98 (0.28–1.56)
30 min (1 % halothane)	0.58 (0.23–1.04)	0.41 (0.20–0.74)	0.85 (0.54–1.79)	0.91 (0.27–1.72)
45 min (1.5 % halothane)	0.67 (0.24–0.94)	0.40 (0.21–0.69)	0.78 (0.50–1.65)	0.93 (0.26–1.46)

TABLE III. *Median (range) first peak latency (ms) in patients receiving halothane or thiopentone*

	Halothane ($n = 6$)		Control ($n = 6$)	
	R leg	L leg	R leg	L leg
Baseline	15.9 (13.7–17.8)	15.8 (14.1–16.7)	15.6 (13.8–15.9)	15.5 (13.1–16.4)
15 min (0.5 % halothane)	16.0 (14.0–16.9)	15.9 (14.4–17.4)	15.7 (14.0–15.9)	15.7 (13.3–16.5)
30 min (1 % halothane)	16.0 (14.7–16.7)	15.9 (14.8–17.6)	15.7 (14.1–16.1)	15.8 (13.6–16.7)
45 min (1.5 % halothane)	16.1 (14.3–18.0)	16.1 (15.1–17.8)	15.8 (14.3–16.1)	15.8 (13.6–16.7)

RESULTS

The administration of increasing concentrations of halothane was associated with a decrease in overall amplitude of the SEP from both legs (table I), but this change was significant only for the left leg after 1.5 % halothane ($P < 0.05$). This significant decline represented only a 25 % change in mean overall amplitude. The control patients who received thiopentone showed only minimal changes in overall amplitude. A similar pattern of response was found for the first peak amplitude (table II) and second peak amplitude (results not shown), but these declines with halothane were not significant. There were no significant changes in first peak latency in either group throughout the study (table III).

Mean arterial pressure decreased progressively in those patients who received halothane, from 86 mm Hg in the baseline period to 62 mm Hg after 1.5 % halothane ($P < 0.05$). In the control group, arterial pressure varied between 90 and 96 mm Hg during the study. There was no significant correlation between overall amplitude and mean arterial pressure ($P < 0.2$).

There were no significant differences between the two groups in overall amplitude, first and second peak amplitudes, and first peak latency throughout the study.

DISCUSSION

The major finding of this study was that halothane in concentrations up to 1.5 % had little effect on the SEP recorded in the extradural space. The only significant observation was a decrease in overall amplitude from the left leg after 1.5 % halothane. Although this finding may be a consequence of the small number of patients studied, unilateral changes in extradural potentials (with minimal cortical changes) have been described, predominantly on the concave side [6]. In the present study we examined patients with idiopathic adolescent scoliosis which was invariably concave to the left. Thus a unilateral effect of halothane on electrophysiological recordings in these patients may be a specific feature of scoliosis. Few studies of SEP have investigated laterality and the common use of concurrent stimulation obscures any potential differences [2]. The only comparable data on the effects of halothane on SEP recorded spinally were obtained in cats [4] and in sheep [7]. In the former case halothane up to 4% had no effect on the SEP recorded from the spinous process, whereas in sheep 2% halothane resulted in a significant attenuation of all components of the SEP recorded subdurally.

The inherent variability of the electrophysiological signal must be considered before any clinical significance is given to a change in SEP during intraoperative monitoring for scoliosis surgery. Overall amplitude varies randomly between 10 and 30% [8], which is similar to the largest change seen with halothane in the present study. Animal studies have shown that a decrease in overall amplitude of more than 50% of the cortical response, or disappearance of a waveform, is likely to be associated with an adverse neurological outcome after operation [4]. In modern clinical practice a decrease in amplitude greater than 30% is considered to merit careful appraisal of the surgical technique [9].

The SEP recorded extradurally has three peaks (fig. 1). The short latency potentials probably reflect post-synaptic conduction in the spinocerebellar tract, while the asynaptic dorsal column fibres conduct more slowly and are responsible for the later potentials. Percutaneous recording of responses evoked by lower limb stimulation is technically more difficult than extradural recording with high impedance and more baseline drift: several thousand responses need to be averaged and the waveform does not show the triphasic potential found extradurally [10].

In conclusion, we can confirm the postulate of Jones and colleagues [3] that the use of halothane is unlikely to alter the interpretation of the SEP recorded extradurally during corrective spinal surgery. A possible unilateral effect of halothane in such patients merits further investigation. The well recognized depressant effects of halothane on cortically recorded SEP [11] do not have a significant spinal component.

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GENERAL ANAESTHETIC MODIFICATION OF SYNAPTIC FACILITATION AND LONG-TERM POTENTIATION IN HIPPOCAMPUS

M. B. MacIVER, D. L. TAUCK AND J. J. KENDIG

There is increasing evidence that general anaesthetics may act at multiple membrane sites to depress excitatory transmission in central nervous system pathways, and that the combination of actions which results in anaesthesia may differ among agents [1–5]. This concept represents a significant departure from "unitary" theories of anaesthetic action which propose a common mechanism at a hydrophobic site for all agents [6–8]. The dissimilar molecular structures exhibited by anaesthetics and the variety of possible sites with which anaesthetics can interact in neuronal membranes provide a high probability that molecular sites of action are different for different agents.

The present study chose two structurally different inhalation agents, a halogenated hydrocarbon (halothane) and a halogenated ether (methoxyflurane) to test this possibility (fig. 1). Rat hippocampal brain slices were chosen as the test preparation because of the ease of controlled extracellular recording of synaptically evoked responses. We examined anaesthetic actions on the CA1 neurone excitatory postsynaptic potential (EPSP) and population spike (PS), with particular attention to the properties of short-term synaptic facilitation of the EPSP, paired-pulse potentiation of the PS (PP), and long-term PS potentiation (LTP). Synaptic facilitation, PP and LTP are three common manifestations of use-dependent changes in neuronal excitability. As such, they may be of importance in anaesthesia, but have not been studied systematically in this regard.

SUMMARY

The synaptic integrative properties of facilitation and potentiation are important determinants of cortical neurone excitability. The present study measured the effects of halothane and methoxyflurane on synaptic facilitation, paired-pulse potentiation, and long-term potentiation (LTP) in CA1 pyramidal neurones of rat hippocampal slices. Methoxyflurane 0.16 vol% and halothane 1.2 vol% depressed population spike amplitudes by approximately 100%, but halothane did so with relatively little (< 10%) depressant effect on the field excitatory postsynaptic potential (EPSP). Both agents enhanced EPSP facilitation, halothane more than methoxyflurane. Halothane consistently enhanced paired-pulse population spike potentiation; methoxyflurane sometimes diminished it. Halothane reduced the probability of LTP induction to an extent correlated with block of population spike responses in the inducing stimulus train (r = 0.92); methoxyflurane did not block LTP. The results suggest that these agents affect cortical excitability by multiple actions, the distribution of actions being specific to each agent.

MATERIALS AND METHODS

Preparation

Experiments were conducted on 52 hippocampal slices from male Sprague–Dawley rats (150–250 g). Studies were limited to one or two concentrations of a single anaesthetic in each slice. Rats were anaesthetized with diethyl ether, the heart stopped by a blow to the back of the thorax, and the brain removed rapidly and placed in precooled (10 °C) artificial cerebrospinal fluid (ACSF) (composition (mmol litre^{-1}): NaCl 134;

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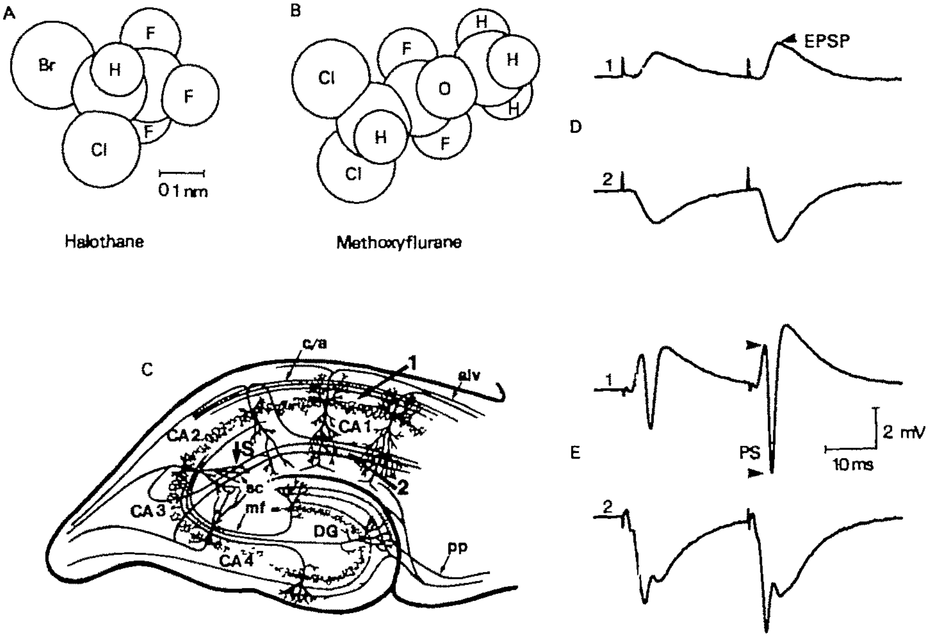

FIG. 1. Space-filling diagrams for halothane (A) and methoxyflurane (B), showing the dissimilar molecular volumes (halothane = 112.09 nm^3; methoxyflurane = 122.29 nm^3) and steric non-conformities of the two anaesthetics. These diagrams were produced using the XICAMM computer-aided molecular modelling system (XIRIS Corp., N.J.) and represent low energy conformations of the anaesthetic molecules. C: Diagram of a hippocampal slice showing placement of stimulating (S) and recording electrodes in the somatic (1) and dendritic (2) areas of Ca1. Recordings of monosynaptically evoked field potentials are shown on the right. D: EPSP produced by low intensity stimuli and recorded at the somatic (1) and dendritic (2) sites. E: Field potentials with population spikes (PS) were produced by higher intensity stimuli. A negative PS is superimposed on the positive EPSP wave form recorded at the somatic site, and a positive PS is superimposed on the negative EPSP at dendritic sites. Note the increase in both EPSP and PS amplitudes following the second of a pair of identical stimuli. CA1–4 = Hippocampal pyramidal neurones; DG = dentate granule neurones; pp = perforant path; mf = mossy fibres; sc = Schaffer collaterals; c/a = commissural/associational fibres; alv = alveus.

KCl 4.5; CaCl$_2$ 1.6; KH$_2$PO$_4$ 1.25; MgSO$_4$ 2; NaHCO$_3$ 16; dextrose 10. This solution was modified from Richards, Russell and Smaje [9] by adjusting calcium and potassium concentrations to correspond to those measured *in vivo* [10].) Following dissection of the dentate–hippocampal formation, transverse slices of hippocampus were cut using a McIlwain tissue chopper (400 u, Mickel Lab. Eng. Co., U.K.). Slices were maintained on a nylon mesh screen at the gas–liquid interface in a chamber based on the design of Richards and Tegg [11]. Oxygenated (95% oxygen–5% carbon dioxide) and pre-warmed (35 °C) ACSF was perfused continuously through the chamber at a rate of 0.5–1.0 ml min^{-1}.

Electrophysiology

A bipolar tungsten stimulating microelectrode was placed on Schaffer-collateral fibres (fig. 1C) to activate electrically the excitatory synaptic inputs to CA1 pyramidal neurones. Similarly, antidromic responses were produced by stimulating axons in the alveus. Extracellular glass fibre-fill recording electrodes (filled with ACSF, resistance 0.5–1.0 MΩ) were placed at the border between stratum pyramidale and stratum oriens (1 in fig. 1C) and in stratum radiatum (2 in fig. 1C) to measure synaptically evoked field potentials at the somatic and dendritic levels, respectively.

Potentiation was defined as the increase in PS amplitude induced by repetitive stimulation. For paired-pulse potentiation experiments (PP), paired stimulus pulses of 0.01–0.05 ms duration (1–12 V) were delivered at 0.08 Hz. Stimulus strength was adjusted to produce half maximal PS on the first pulse.

Facilitation was defined as the increase in EPSP amplitude induced by repetitive stimulation. For facilitation experiments, trains of four stimuli at 20 Hz were applied at intensities subthreshold for PS generation. Interpulse interval was set to 24 ms for PP, and 48 ms for facilitation experiments; these parameters produced optimal facilitation and potentiation in control experiments.

Both PP and facilitation are of brief duration (~500 ms), while LTP is the increase (hours to days duration) in PS amplitude induced by a longer stimulus train. Single stimulus trains of 50 Hz for 500 ms were used to induce LTP. Recorded signals were amplified (× 1000), filtered (1 Hz to 10 KHz, bandpass), and stored digitally for later analysis. Records shown are averages of 10 individual field potentials recorded at 0.08 Hz.

EPSP amplitude was chosen in place of rate of rise as a measure of synaptic transmission for two reasons: the use of stimuli subthreshold for PS generation permitted an independent measure of this parameter, uncomplicated by discharge of CA 1 neurones; and in the case of supra-threshold stimulation, the potentiated PS often reduced the rising phase of the EPSP, preventing accurate measurements of rate of rise. EPSP amplitude at the soma was measured as the peak positivity and in the dendritic region as the peak negativity (fig. 1D). PS amplitude was measured from threshold to peak negativity (arrowheads in fig. 1E). Data were standardized as percent of control amplitudes for concentration–response analysis.

Control and drug responses were compared using the Wilcoxon two-tailed test.

Administration and analysis of anaesthetics

Halothane and methoxyflurane were applied as vapours via the pre-warmed and humidified oxygen–carbon dioxide gas stream above the slices, using calibrated commercial vaporizers (Foregger, U.S.A., mod. DRV 1; Cyprane, U.K., mod. MK II). Vapour concentrations were applied for a minimum period of 30 min, to ensure that equilibrium was achieved. Steady-state effects on PS amplitudes were observed consistently after 20 min for all concentrations studied. Particular care was taken to examine concentrations relevant to anaesthesia (halothane MAC = 1.2 vol% and methoxyflurane MAC = 0.16 vol%, in rat) [12].

Accurate measurements of anaesthetic concentrations in the vapour phase were obtained using an infra-red absorption monitor (Puritan-Bennett Co., U.S.A., mod. AAM222). Sample gas was drawn continuously from the tissue chamber at a site 1.0 mm above the tips of the stimulating electrode placed in the brain slice studied. Chamber concentrations reached equilibrium within 5–10 min of adding the anaesthetic to the gas stream. An approximation of ACSF concentrations of halothane (in mmol litre^{-1}) can be obtained from MacIver and Roth [13].

Halothane was obtained from Ayerst Laboratories Inc., U.S.A., and methoxyflurane from Abbott Laboratories, U.S.A. All chemicals were reagent grade or better and were obtained from J. T. Baker Chemical Co., U.S.A.; water for solutions was "tissue culture" grade obtained from Dr J. R. Trudell (Stanford University Medical Center).

RESULTS

Anaesthetic-induced depression of evoked discharge

Methoxyflurane and halothane produced a marked depression of the synaptically evoked population spike recorded from CA 1 pyramidal neurones (fig. 2). Concentrations which correspond to 1 MAC for each agent reduced CA 1 evoked discharge to 2.7 (SD 3.1)% and 1.0 (6.3)% of control for methoxyflurane 0.16 vol% and halothane 1.2 vol%, respectively. Halothane was consistently more effective at blocking PS responses to a single stimulus (ED_{50} = 0.25 vol%) than the facilitated PS response to the second of a pair of stimuli (ED_{50} = 0.54 vol%) (fig. 2B). Methoxyflurane produced greater depression of the facilitated than the single PS response in some experiments (five of 18; e.g. fig. 2A); however, in most experiments the response to a single stimulus was more sensitive to this agent also. Concentration–response graphs for depression of PS responses to a pair of stimuli of equal strength are shown on the right of figure 2. The mean (SD) difference in sensitivity between the first and second response across the effective concentration range was 28.3 (3.64)% for halothane and 19.9 (8.4)% for methoxyflurane.

Comparison of effects on EPSP v. *PS discharge*

Effects on evoked dendritic and somatic field potential responses were compared, to determine if the anaesthetic-induced depression of PS responses was a result of block of excitatory transmission at the synapse or of depression of spike initiation in the postsynaptic neurones. The dendritic field potential is composed predomi-

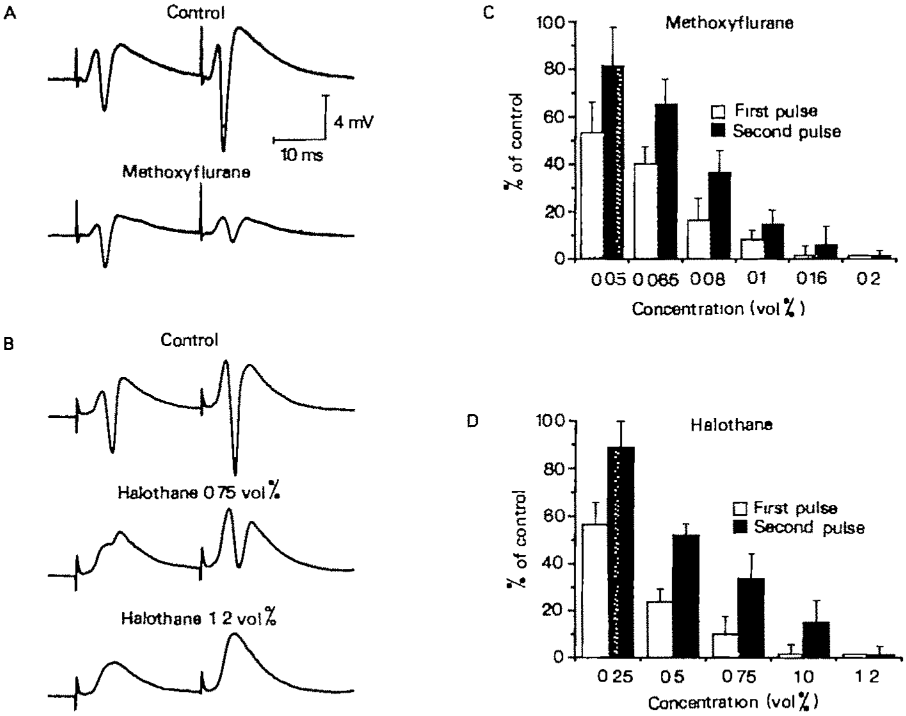

FIG. 2. Methoxyflurane and halothane produced a concentration-dependent depression of evoked field potential amplitudes. A: Block of paired-pulse potentiation produced by methoxyflurane which accompanied depression of field potentials in this experiment. B: Effect produced by halothane; this agent did not decrease paired-pulse potentiation of PS responses in any experiment. Concentration–response bar graphs for methoxyflurane (C) and halothane (D): each point represents the mean (SD) from at least three experiments. A comparison of effects produced on the amplitude of evoked PS responses to the first and second of a pair of stimuli is shown.

nantly of the EPSP, while the potential recorded at the soma reflects the population spike [14]. As shown in figure 3, both agents produced a greater reduction in field potential amplitudes recorded at the somatic than at the dendritic level. In this experiment, halothane 1.2 vol % produced a marked reduction in PS amplitude (> 90 %) with only a slight depression (< 10 %) of field EPSP responses recorded at the dendritic site. Methoxyflurane 0.16 vol % produced a more pronounced depression of field EPSP responses (> 15 %), but the major effect of this agent also appeared to involve a depression of postsynaptic excitability (PS responses reduced to < 30 % of control). For halothane, the depression of discharge was accompanied by an increase in threshold, measured as the point of PS initial inflection on the EPSP (fig. 3B). This was not the case for methoxyflurane, which decreased PS threshold (fig. 3A). In the presence of 1 MAC of either anaesthetic, the depression of synaptically evoked PS potentials was attributed to a reduction in the number of CA1 neurones discharging, or to a smaller discharge current produced in each cell. In this regard, it is interesting that neither halothane nor methoxyflurane altered PS responses to antidromic stimuli at 1 MAC.

Effects on facilitation of field EPSP responses

Examination of the dendritic field EPSP responses in the presence of the anaesthetics suggested that facilitation of synaptic transmission may have been increased by both halothane and methoxyflurane (fig. 3). EPSP responses to a short train of stimuli (four pulses at 20 Hz) were studied to determine if facilitation was increased by these agents. In the presence of 1 MAC of either anaesthetic, EPSP facilitation was increased (fig. 4). Halothane increased facilitation by 44 % and methoxyflurane increased it by 15 %. The increase in facilitation was sufficient to overcome the anaesthetic-induced depression of EPSP

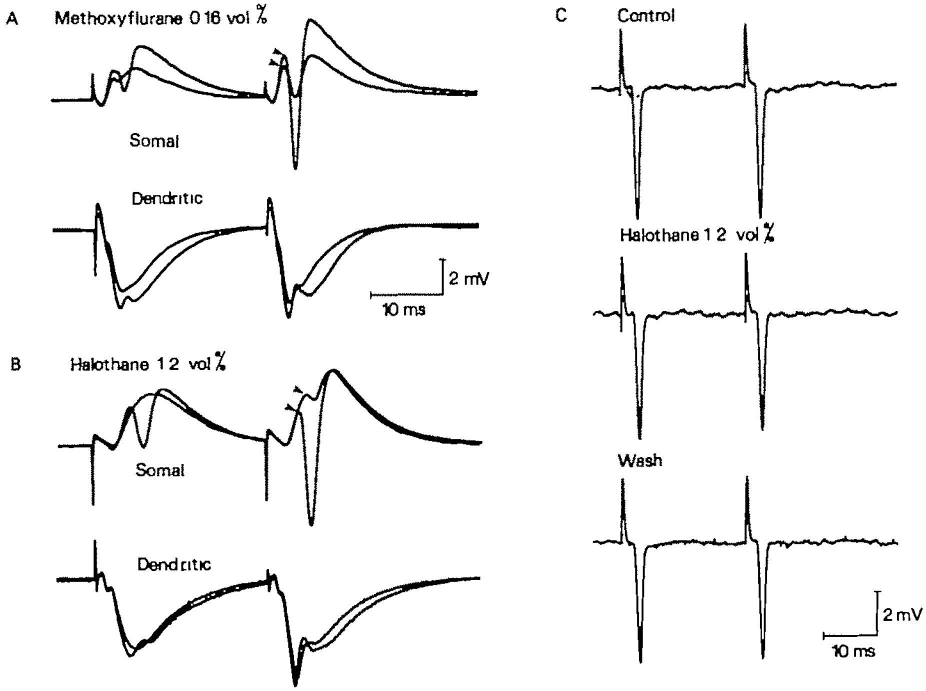

FIG. 3. Comparison of effects on dendritic field EPSP potential and PS. Methoxyflurane (A) depressed EPSP responses recorded at both the somatic and dendritic sites, an effect which would contribute to the depression of PS amplitudes. In contrast, halothane (B) produced a marked depression of PS amplitudes measured at the somatic recording site, but only a slight depression of field EPSP responses recorded at the dendritic site.

responses with 1 MAC of halothane; however, PS responses never approached control levels, even at high frequencies of stimulation (e.g. fig. 6). The increase in EPSP facilitation could account for the difference in anaesthetic potency between the first and second PS responses described above (fig. 2, fig. 3A, B).

Effects on long-term potentiation

Figure 5 illustrates the experimental procedure used to study anaesthetic effects on long-term potentiation (LTP) of synaptic responses. When a stable (<5 % variability/30 min) control response was obtained, the anaesthetic was applied for at least 20 min to achieve steady-state effects on PS amplitudes. An LTP-inducing stimulus train (50 Hz, 500 ms) was applied while the anaesthetic was still present and responses were monitored for an additional 20 min. During this time, potentiation was often observed as an increase in the anaesthetic-depressed field potential amplitude; a further increase occurred following washout of the anaesthetic (dashed line in figure 5). LTP was considered to have been evoked if PS amplitudes remained greater than 110 % of pre-anaesthetic control for at least 1 h after washout.

Even high concentrations (e.g. 0.2 vol %) of methoxyflurane did not alter significantly the probability of producing LTP (16 of 18 experiments; probability = 0.89; $P > 0.05$) compared with control experiments (14 of 16 experiments; probability = 0.88). In contrast, halothane reduced significantly the probability of producing LTP (probability = 0.5 at 1.2 vol %; $n = 6$; $P < 0.01$). The effect of halothane on probability of LTP induction is shown at the top right of figure 6. All concentrations greater than 0.25 vol % produced comparable depression of LTP induction.

The depression of LTP produced by halothane was correlated with the presence of PS response during the LTP-inducing stimulus train. As shown on the left side of figure 6, in control conditions the stimulus train elicits population spikes in response to each pulse during the train. In the presence of either anaesthetic, PS responses were nearly abolished after the first few pulses of the stimulus train. Halothane may depress LTP

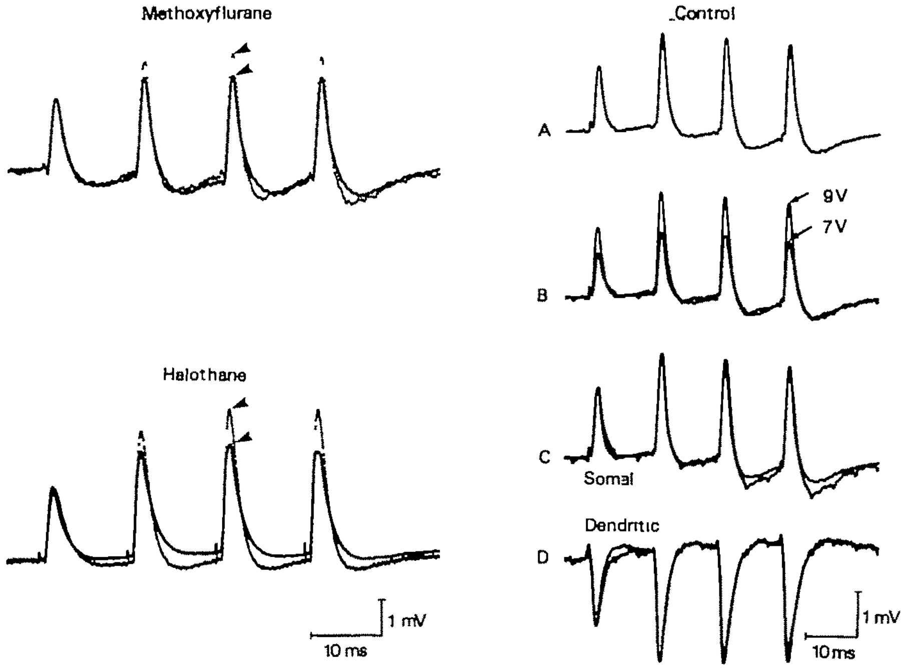

FIG. 4. Comparison of effects on EPSP facilitation. Anaesthetic effects on synaptic facilitation were studied on EPSP responses to a train of stimuli, subthreshold for discharging the CA1 pyramidal neurones. Responses in the presence of anaesthetic (dotted lines) have been scaled to match the first pulse EPSP amplitudes of pre-drug control records (solid lines). Both anaesthetics increased EPSP facilitation (arrowheads).

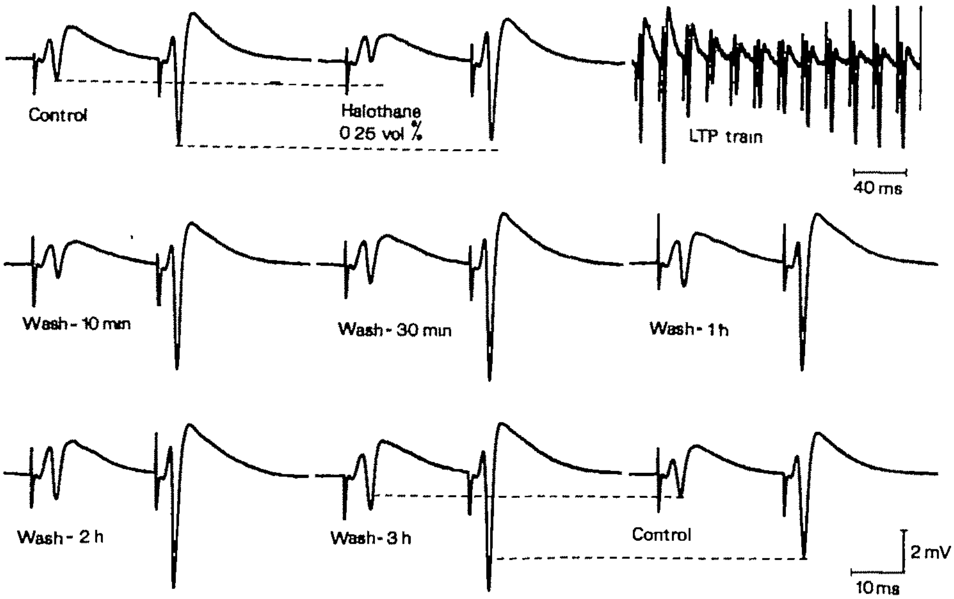

FIG. 5. Evoked field potentials produced by paired stimulus pulses recorded at the somatic site are shown to illustrate the experimental procedure for long-term potentiation (LTP) studies. The anaesthetic (in this case 0.25 vol% halothane) was applied for a minimum of 20 min to achieve equilibrium before an LTP-inducing train of stimuli (50 Hz, 500 ms) was provided. In many experiments LTP was observed within 5–10 min following the LTP stimulus train, but was most evident following washout (compare responses after 3 h of wash with the pre-anaesthetic control—dashed lines at the lower right).

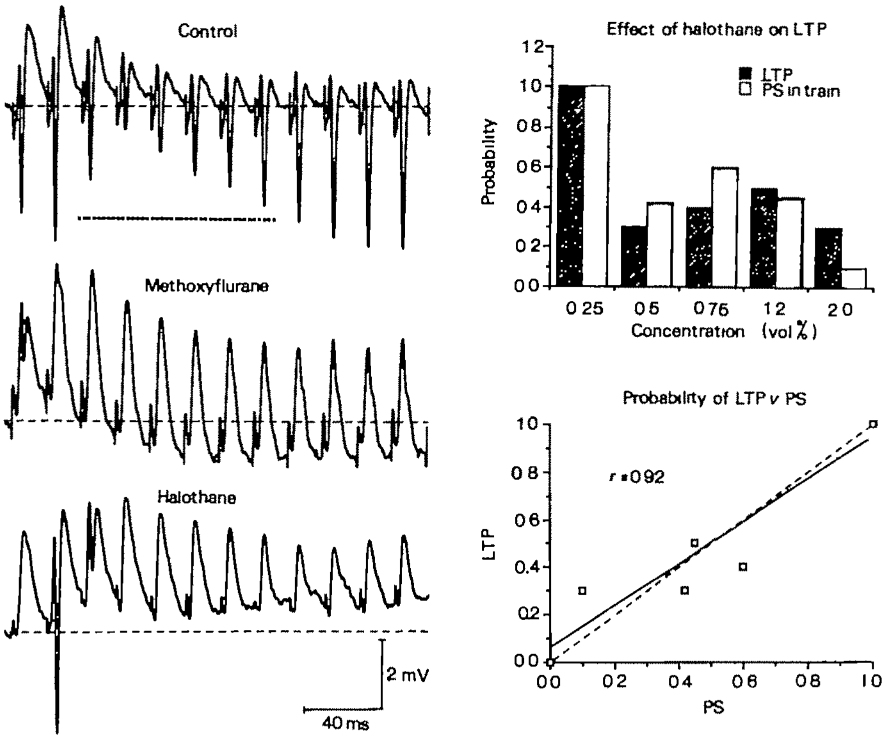

FIG. 6. Field potential recordings during LTP-inducing stimulus trains are shown on the left. Note the period of apparent inhibition (dotted line under the control record) when PS responses are depressed relative to the first two pulses. In the presence of methoxyflurane 0.2 vol % only minimal discharge was observed (PS on first pulse); however, LTP was produced. In contrast, LTP was blocked by halothane 0.5 vol % when PS responses during the LTP-inducing train were depressed. The relation between the occurrence of PS responses during the LTP train and the subsequent probability of LTP development in the presence of increasing concentrations of halothane is shown in the bar graph. The correlation between the occurrence of PS during the train and subsequent induction of LTP is shown in the graph (solid line = linear regression; dashed line = line of unity).

induction by blocking postsynaptic discharge since, in the presence of this agent, the probability of LTP was correlated with the presence of PS responses during the inducing train ($r = 0.92$; lower right of figure 6). Figure 6 illustrates the marked difference between methoxyflurane and halothane with respect to LTP induction. LTP was produced in the presence of 0.2 vol % methoxyflurane, but not in the presence of 0.5 vol % halothane, even though methoxyflurane produced a greater depression of discharge during the LTP-inducing train.

DISCUSSION

Anaesthetic-induced depression of synaptic transmission

Both anaesthetics in the present study produced a marked depression of CNS synaptic transmission as measured by PS amplitude (fig. 7). Concentrations equivalent to 1 MAC for both agents significantly blocked synaptically evoked discharge of the hippocampal CA 1 population in response either to a single stimulus or to a paired stimulus which evoked a potentiated response (dashed line in figure 7). These results support previous observations that hippocampal cortical neurones are sensitive to both volatile and barbiturate general anaesthetics at clinically relevant concentrations [2, 13–16], as are neurones in olfactory cortical slices [10, 17]. The sensitivity of both tissues lends support to the proposal that cortical excitatory transmission is depressed during anaesthesia [18].

Differential effects of anaesthetics on evoked responses

Although both anaesthetics produced a depression of the singly evoked PS, the mech-

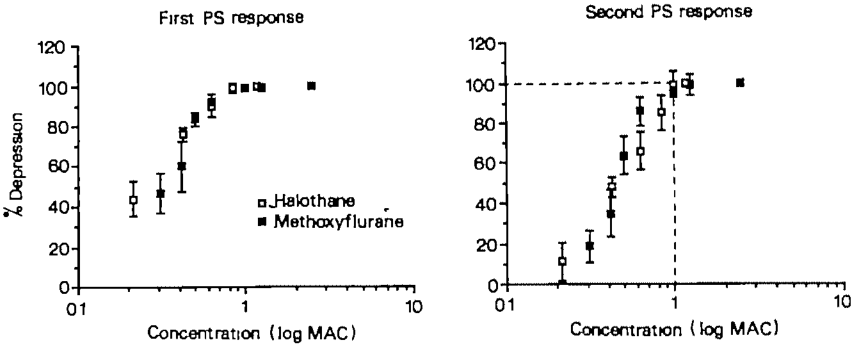

FIG. 7. Concentration–response curves for halothane and methoxyflurane on synaptically-evoked PS responses to the first and second of a pair of stimuli; 1 MAC of both anaesthetics produced marked depression of discharge (dashed line). Each point represents the mean (SEM) from at least three separate experiments.

anisms underlying this effect appeared to differ between the agents. Halothane depressed postsynaptic spike discharge by a predominantly non-synaptic action indicated by the marked depression of PS amplitudes with little effect on EPSP responses (fig. 3) [see also: 13, 19, 20]. This postsynaptic depressant action of halothane resembles, to some degree, the effects produced by barbiturates on this synaptic pathway [16], particularly with respect to the apparent increase in discharge threshold (arrowheads in fig. 3B). In contrast, methoxyflurane depressed EPSP responses, which contributed to the observed reduction of PS amplitudes. In this regard, methoxyflurane resembles closely the related halogenated ether anaesthetics, isoflurane and enflurane, which also depress EPSP responses at concentrations which reduce PS amplitudes [13]. Methoxyflurane also resembles enflurane in reducing the threshold for PS generation (figs 2, 3); but, unlike the effect of enflurane, the reduction in discharge threshold was not sufficient to produce spontaneous or evoked burst firing of the CA1 population [15]. The differential effects produced by methoxyflurane and halothane, summarized in table I, provide further support for discrete anaesthetic-specific interactions with membrane recognition sites [21].

Effects on EPSP facilitation and paired-pulse potentiation

Halothane produced a greater depression of PS responses to the first compared with the second of a pair of stimuli (fig. 2). The difference in sensitivity between the two responses could be accounted for by the observed increase in EPSP facilitation produced by halothane (figs 3, 4). Anaesthetic-induced increases in facilitation are observed also at the crustacean neuromuscular junction [22], in which facilitation is presumed to be a property of the presynaptic nerve terminal. Halothane effects on PS responses to a pair of stimuli may be explained by postulating that halothane increases both EPSP facilitation and the threshold for spike initiation [20]. On the other hand, methoxyflurane also increased EPSP facilitation but reduced PS potentiation in 28% of experiments (e.g. fig. 2). These apparently contradictory findings might be explained if methoxyflurane, in common with barbiturates [16, 23], significantly increased intrinsic or synaptic inhibitory currents which limit the ability of neurones to generate repetitive impulses [24, 25]. Evidence suggestive that halothane and

TABLE I. *Comparison of anaesthetic effects at 1 MAC on synaptic transmission, facilitation and potentiation. PS = population spike; EPSP = excitatory postsynaptic potential; PP = paired-pulse potentiation of the PS (depression of first PS relative to second PS); LTP = long-term potentiation (probability of inducing LTP relative to control). *Percent depression of pre-anaesthetic control amplitude. †Methoxyflurane depressed second PS response more than the first in 28% of experiments. ‡Antidromic PS responses were not altered by either anaesthetic*

Response	Halothane	Methoxyflurane
PS (% depression)*	↓↓↓100	↓↓↓97.3
EPSP (% depression)*	↓<10	↓↓>15
EPSP facilitation (%)	↑↑44	↑15
PP potentiation (%)	↓30	↓↓20†
LTP (△ probability)	↓0.57	−1.01
Antidromic‡	—	—

methoxyflurane differ in this respect is provided by the observation that the two agents induce opposite shifts in the baseline during high frequency stimulus trains (fig. 6).

Effects on long-term potentiation

The two anaesthetics had markedly different effects on LTP induction. Halothane produced a reduction in the probability of occurrence of LTP which correlated well with the anaesthetic-induced depression of PS responses during the stimulus train (fig. 6), while methoxyflurane did not block LTP. Both calcium entry and depolarization are normally required for the expression of LTP [26,27]. Halothane-induced block of LTP may be attributed to reduced postsynaptic depolarization; however, methoxyflurane acts at pre- or postsynaptic sites, or both, to preserve LTP induction despite a comparable depression of discharge. The i.v. anaesthetics ketamine and phencyclidine also block LTP, but by a different mechanism which involves inhibition of the NMDA receptor–calcium ionophore [28,29].

Membrane actions of anaesthetics

The differential actions produced by halothane and methoxyflurane (table I) are not compatible with a common effect at identical membrane sites, as required by unitary theories of anaesthetic action [7,8]. Because these agents exhibit different molecular properties such as size, volume and charge distribution (fig. 1), they bind to different membrane microdomains composed of heterogeneously distributed proteins (e.g. neurotransmitter receptors and ion channels) [30] and associated lipids [31–33]. Results of the present study demonstrate agent-specific actions at sites which discriminate between the molecular structures of inhalation anaesthetics.

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EFFECT OF ANAESTHETIC AGENTS ON BILE FLOW AND BILIARY EXCRETION OF ^{131}I-CHOLYLGLYCYLTYROSINE IN THE RAT†

C. O. MILLS, J. F. FREEMAN, P. J. SALT AND E. ELIAS

SUMMARY

We have compared in the rat the effects of i.v. anaesthetic agents on bile flow rate and on the biliary excretion of a novel bile acid, ^{131}I-cholylglycyltyrosine (^{131}I-cholylgly.tyr.). Etomidate 1-mg bolus and 2-mg h^{-1} infusion, Althesin 3-mg bolus and 14.5-mg h^{-1} infusion and propofol 3.3-mg bolus and 3.3-mg h^{-1} were given via a tail vein cannula and pentobarbitone 50 mg kg^{-1} was given by the intraperitoneal route, to groups of six rats. Each animal received only one anaesthetic agent. One hour after cannulation of the common bile duct, ^{131}I-cholylgly.tyr. 5 μCi was injected into the jugular vein and bile was collected every 1 min for 10 min. The mean (SD) percentage cumulative biliary excretion of ^{131}I-cholylgly.tyr. at the end of 10 min was: propofol group 74.1 (5.2)%; Althesin group 82.3 (2.2)%; etomidate group 69.4 (17.6)%; pentobarbitone group 76.4 (3.2)%. Propofol and Althesin were relatively more choleretic, causing bile flow rates twice that produced by pentobarbitone. Only Althesin caused a significant increase in biliary excretion of ^{131}I-cholylgly.tyr. relative to that in rats that received pentobarbitone. Bile flow rates for the respective anaesthetic techniques (μl min^{-1}/100 g body weight) (mean (SD)) were: propofol group 14.1 (1.8); Althesin group 12.5 (1.7); etomidate 8.5 (1.4); pentobarbitone group 7.3 (1.0). There was a marked metabolic acidosis in all rats except in the propofol group, in which normal acid–base status and oxygenation were observed.

Anaesthetic agents used in animal research and clinically in patients may affect hepatobiliary function. Such agents used commonly include pentobarbitone, a barbiturate which has been used widely in hepatobiliary studies in the belief that it does not affect bile formation in the bile fistula rat [1–3]. This view was challenged recently [4]. Paumgartner and colleagues [5] have reported that another oxybarbiturate, phenobarbitone, increased bile flow in the rat, whilst Klaassen [6] reported that pentobarbitone may not be suitable for studies investigating the biliary excretion of drugs because its metabolism produces polar metabolites which compete for the hepatic transport of the drugs under investigation. Similarly, it has been reported that pentobarbitone anaesthesia should be used with caution while studying the effect of other agents on the rate of bile secretion [7]. This was confirmed in a study which reported that pentobarbitone diminished the hepatic transport of succinylsulphathiazole into the bile [8]. Other anaesthetic agents unsuitable for studies involving the biliary excretion of drugs include ether, which produced acidosis in the isolated rat liver [9] and chloralose [9].

Because of these conflicting reports we have investigated the effect of anaesthetic agents on bile flow and biliary excretion of ^{131}I-cholylglycyltyrosine (^{131}I-cholylgly.tyr.). This novel bile acid has a very high first pass liver uptake, similar to that of the natural bile acid taurocholate [10], thus providing an index of hepatobiliary transport [11] under different anaesthetic conditions. We

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studied Althesin, which is excreted in bile (70%) and urine (30%) [12–14], etomidate (urine (78%) and bile (13%) [15]), pentobarbitone (urine (72%) and bile (28%) [6]; metabolized in the liver before renal excretion [16]) and propofol (Diprivan) (kidneys (88%) and bile (2%) [17]).

MATERIALS AND METHODS

Materials

Pentobarbitone was obtained from May and Baker Ltd, Dagenham, Essex; Diprivan from ICI plc, Pharmaceutical Division, Macclesfield, Cheshire; etomidate from Janssen Pharmaceutical Ltd, Grove, Oxford; and Althesin from Glaxo Ltd, Harefield, Uxbridge. Portex polythene tubing was obtained from A. R. Horwell Ltd, London. ^{131}I-cholylgly.tyr. was synthesized in our laboratory as described elsewhere [10].

Animal studies

Four groups each of six male Wistar rats (220–250 g) were anaesthetized with different anaesthetic induction agents. Pentobarbitone 50 mg kg^{-1} was given by the intraperitoneal (i.p.) route. The other agents were given i.v. as a bolus injection followed by a constant infusion via a tail vein cannula: etomidate 1-mg bolus over 1 min followed by 2-mg h^{-1} infusion; Althesin 3-mg bolus, 14.5-mg h^{-1} infusion; propofol 3.3-mg bolus, 3.3-mg h^{-1} infusion. After anaesthesia was established in each rat, laparotomy was performed and the common bile duct was cannulated with polythene tubing, after which the abdomen was closed using a suture. All animals were allowed to breathe room air spontaneously and, 1 h after induction of anaesthesia, the jugular vein was exposed and ^{131}I-cholylgly.tyr. 5 µCi was injected in a volume of 200 µl of physiological saline. Bile was collected in pre-weighed tubes every 1 min for 10 min.

The aorta was cannulated using a 14-gauge cannula with injection valve and a Teflon catheter, and aortic blood samples were obtained after 1 h for analysis of acid–base balance and oxygenation using an ABL blood-gas machine (Radiometer, Copenhagen).

Measurements

The radioactive content of each bile aliquot (^{131}I-cholylgly.tyr.) was determined by counting in a SP500 gamma counter and expressed as percentage of the dose administered. Summation of the dose in each tube gave the cumulative percentage of dose in bile in 10 min.

Bile was collected from the biliary fistula of the animals for the time intervals indicated for each experiment. Bile volume was measured and expressed as µl min^{-1}/100 g body weight.

Statistical analysis

All results are expressed as mean (SD). Student's *t* test was used to determine the significance of differences between means.

RESULTS

Althesin and propofol produced the highest bile flow rates, which were significantly greater than that seen with pentobarbitone ($P < 0.001$). There was no significant difference between etomidate and pentobarbitone (fig. 1).

There was no significant difference in the cumulative biliary excretion of ^{131}I-cholylgly.tyr. between etomidate or propofol and pentobarbitone, but excretion was greater in Althesin treated rats ($P < 0.01$) (fig. 2).

A summary of biliary kinetics of ^{131}I-cholylgly.tyr. is shown in table I. Mean peak excretion rates for the different agents were 12–18% of

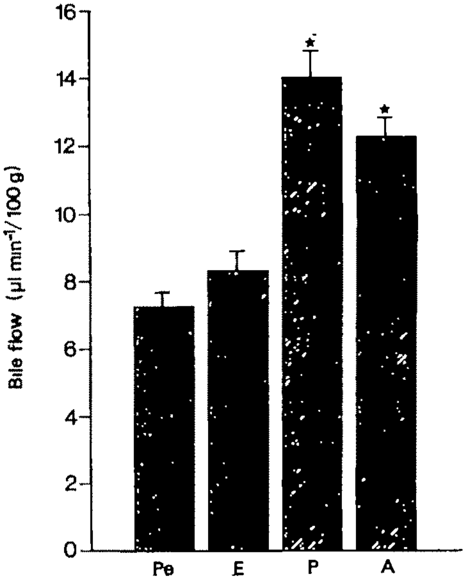

FIG. 1. Bile flow by collection from biliary fistula rats ($n = 6$) in pre-weighed tubes every 1 min for 10 min. Volume is mean (SD) expressed as µl min^{-1}/100 g body weight. Pe = Pentobarbitone; E = etomidate; P = propofol; A = Althesin. *$P < 0.001$.

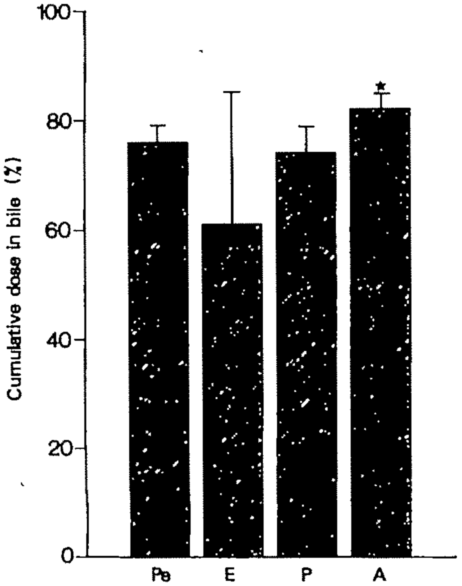

FIG. 2. Biliary excretion of ^{131}I-cholylgly.tyr. (see text). Values are mean (SD); $n = 6$. Pe = Pentobarbitone; E = etomidate; P = propofol; A = Althesin. *$P < 0.01$.

injected dose per minute. There was no significant difference between the values for the different agents. Peak excretion rates occurred at 3 min for propofol and etomidate and at 4 min for pentobarbitone and Althesin. The 50% biliary retention time was computed from a linear correlation of the logarithm of the cumulative dose in bile against different time intervals between 1 and 4 min and extrapolation of the straight line to give the time for the first 50% of the total biliary excretion; it occurred between 4 and 5 min for all agents, with no significant difference between propofol, etomidate or Althesin and pentobarbitone. Only Althesin produced a cumulative percentage dose in bile in 10 min which was significantly different from that of pentobarbitone ($P < 0.01$) (table I).

Only propofol was associated with normal acid–base status and oxygenation. Pentobarbitone approached normal values, whereas etomidate and especially Althesin caused a metabolic acidosis (table II).

TABLE I. *Biliary kinetics of* ^{131}*I-cholylgly.tyr. (mean (SD))*. n = 6. *$P < 0.01$; **$P < 0.001$

Anaesthetic agent	Peak excretion (% dose min^{-1})	Cumulative dose in bile in 10 min (%)	50% Biliary retention (min)	Bile flow (µl min^{-1}/100 g)
Pentobarbitone	17.0 (1.4)	76.4 (3.2)	4.6 (0.04)	7.3 (0.3)
Etomidate	12.6 (8.3)	69.4 (17.6)	4.8 (0.05)	8.5 (0.5)
Propofol	17.6 (2.4)	74.1 (5.2)	4.5 (0.03)	14.1 (0.6)**
Althesin	18.0 (1.9)	82.3 (2.2)*	4.5 (0.05)	12.5 (0.05)**

TABLE II. *Mean (SD) acid–base and blood-gas status.* n = *6 for each agent. BE = Base excess; SBE = standard base excess; SBC = standard base concentration*

	Pentobarbitone	Etomidate	Althesin	Propofol
Temp. (°C)	37.00 (0.50)	37.50 (0.60)	37.00 (0.50)	37.50 (0.50)
Hb (g dl^{-1})	14.07 (5.38)	16.03 (0.84)	15.87 (1.39)	13.83 (4.00)
pH	7.37 (0.03)	7.34 (0.07)	7.29 (0.03)	7.37 (0.01)
$P\text{CO}_2$ (kPa)	5.70 (0.84)	5.56 (0.64)	5.38 (0.55)	5.94 (0.07)
$P\text{O}_2$ (kPa)	9.12 (2.20)	8.86 (0.84)	8.24 (0.54)	9.07 (1.21)
HCO_3(mmol litre^{-1})	24.30 (3.30)	21.83 (3.25)	18.73 (0.98)	25.00 (0.64)
BE (mmol litre^{-1})	−0.70 (2.91)	−3.73 (4.08)	−7.33 (0.74)	0.00
SBE (mmol litre^{-1})	−0.57 (2.96)	−4.13 (2.80)	−6.80 (0.78)	0.00
Saturation (%)	89.73 (5.11)	90.10 (0.28)	86.97 (1.45)	91.10 (2.40)
SBC (mmol litre^{-1})	23.90 (2.38)	21.23 (3.20)	18.27 (0.54)	23.87 (0.63)

DISCUSSION

We have studied two anaesthetic agents which are excreted mainly via the kidneys [15, 17], one which is excreted mostly by the liver [12–14] and pentobarbitone, which is excreted via both routes [6]. Pentobarbitone was administered i.p., whereas the other agents were given i.v., and this may have resulted in a different pattern of haemodynamic and ventilatory changes in the animals. However, evidence suggests that a similar biochemical profile was produced after administration of pentobarbitone either 50 mg kg^{-1} i.p. or 35 mg kg^{-1} i.v. Furthermore, the cumulative biliary excretion within 6 h was similar for either i.v. or i.p. administration of pentobarbitone [6, 7].

We have used the i.p. route because it is that used commonly for anaesthetic induction with pentobarbitone in hepatic transport studies. Althesin, which is known to be excreted in bile, caused a significant increase in bile flow compared with pentobarbitone, an effect which is compatible with an osmotic drag of fluid into bile in response to the presence of the drug. As anticipated for an agent excreted predominantly in urine, etomidate did not cause an increase in bile flow rate compared with pentobarbitone. However, propofol, which in common with etomidate is believed to be excreted mainly via the kidneys, caused a significant increase in bile flow rate relative to pentobarbitone (fig. 1). This propofol-induced choleresis would be compatible with an osmotic choleresis caused by active transport of propofol, its metabolites, or both, from the liver into the lumen of the biliary canaliculi [18, 19], as described for Althesin. Of the agents studied, etomidate and Althesin resulted in a greater deviation from normal acid–base status and oxygenation than did pentobarbitone, whereas propofol maintained normal acid–base status and oxygenation (table II). It was surprising that a diminution in bile flow rate resulting from acidosis which has been reported with ether [20] was not observed with Althesin. The biliary excretion of ^{131}I-cholylgly.tyr. in rats treated with the different anaesthetic induction agents (fig. 2) demonstrated that the cumulative percentage dose in bile over 10 min was similar for etomidate, propofol and pentobarbitone. However, there was a slight but significant difference between pentobarbitone and Althesin, suggesting that Althesin-induced choleresis may enhance the biliary output of ^{131}I-cholylgly.tyr., which is a bile salt derivative.

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MATERNAL OXYGENATION DURING NORMAL LABOUR

P. N. REED, A. D. COLQUHOUN AND C. D. HANNING

SUMMARY

Arterial oxyhaemoglobin saturation (Sa_{O_2}) was monitored continuously during normal labour in 33 healthy parturients receiving pethidine and nitrous oxide for analgesia. Sixteen (49%) had episodes exceeding 10 s duration when Sa_{O_2} was $<90\%$ (mean 83.7%, range 89–60%). Two women had multiple episodes of profound hypoxia with $Sa_{O_2} < 70\%$.

Hypoxia occurring during labour may be harmful to both mother and baby, particularly if placental blood flow is impaired. Maternal oxygenation may be influenced by the analgesic drugs commonly administered during the first and second stages of labour.

The aim of this study was to determine the frequency and severity of maternal hypoxia during normal labour.

METHODS AND RESULTS

Caucasian women with normal medical and obstetric histories, who did not intend to request extradural analgesia, gave written consent to this prospective study approved by the District Ethics Committee. Pethidine 100–150 mg i.m. and self-administered Entonox (50% nitrous oxide in oxygen) (first stage only) were given in the manner usual for analgesia.

Maternal Sa_{O_2} was measured continuously using a pulse oximeter (Ohmeda Biox III or 3700) attached to an earlobe and was recorded with fetal heart rate and uterine contractions (Sonicaid, Hewlett-Packard) on a multichannel pen recorder. Obstetric events and analgesic administration were recorded.

Sa_{O_2} values $<90\%$ persisting longer than 10 s were regarded as indicative of significant maternal hypoxia.

Forty-one women entered the study. Five who subsequently received extradural analgesia and three who delivered within 1 h were excluded. The remaining 33 parturients were monitored for a total of 125 h (mean 3.8 h, range 1.0–9.9 h), and all received pethidine and or Entonox during part of their labour.

Although the modal baseline Sa_{O_2} was 98% (range 97–100%), a total of 84 episodes of significant hypoxia were recorded. These occurred in 16 women: nine of 20 mothers receiving pethidine and Entonox; two of seven mothers receiving pethidine alone; and five of six mothers receiving Entonox alone. This difference was not statistically significant using a Chi-square test with Yates' correction.

Hypoxic episodes were noted in both the first and second stages of labour: 11 women in the former, usually towards its end, three in the latter and two in both stages. The episodes of hypoxia noted when the mothers were given no analgesia, pethidine or Entonox, or the combination, during the first and second stages of labour are shown in table I. There was no significant difference between the groups.

The mean Sa_{O_2} of each episode was 83.7% (range 89–60%) and the mean duration was 31.2 s (range 10–130 s). The mean total duration of hypoxia in any parturient was 165 s (range 20–1125 s)—a small proportion of their total labours. However, two women were profoundly hypoxic at some times. One primigravid was hypoxic intermittently for a total of 18.75 min, with a minimum recorded saturation of 61%;

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TABLE I. *Duration of monitoring and hypoxaemia while parturients were receiving different analgesics during the first and second stage of labour. Hypoxaemia expressed as number of parturients experiencing one or more episodes of hypoxaemia, total number of episodes and mean number of episodes per parturient and per hour of recording. Total number of parturients = 33. Some individuals are included in more than one analgesic regimen*

	n	Duration of monitoring (min)	Number hypoxic	Hypoxic episodes	Number of episodes per parturient	Number of episodes per hour
First stage						
No analgesia	23	2452	1	2	0.087	0.049
Entonox only	7	520	3	5	0.71	0.57
Pethidine only	21	1677	5	12	0.57	0.43
Pethidine + Entonox	20	1819	8	41	2.05	1.4
Second stage						
No analgesia	6	200	3	18	3.0	5.4
Following pethidine	27	808	2	6	0.22	0.44

another was hypoxic for a total of 6.5 min, with a lowest saturation of 60%. Neither woman had hypoxic episodes before analgesia was commenced (33 and 67 min of monitoring, respectively). Hypoxic episodes (four in 32 min and one in 106 min) commenced after the administration of pethidine. The numbers of episodes noted during the coincident administration of Entonox were 18 in 178 min and nine in 44 min, respectively. No abnormality was noted in the uterine contractions at any time. Hypoxic episodes were not seen during the second stage, and both women delivered healthy babies with Apgar scores of 8 at 1 min and 10 at 5 min.

Maternal hypoxia occurred usually between contractions in the first stage of labour. The onset was generally 1–2 min after the peak of a contraction and was terminated by the onset of the next. During the second stage, hypoxia occurred usually during contractions.

There was no significant difference in the parity, age or weight of the mothers having hypoxic episodes compared with those who did not. There was no difference in the rates of augmentation or induction of labour, uterine contraction abnormalities or instrumental delivery. One baby whose mother had been hypoxic had Apgar scores of 6 at 1 min and 9 at 5 min. All other babies had Apgar scores of 8 or more.

COMMENT

Huch and colleagues, using transcutaneous measurement of oxygen tension (Ptc_{O_2}) in both mother and fetus, demonstrated that a reduction in maternal Ptc_{O_2} to less than 9.3 kPa (Sa_{O_2} approximately 90%) resulted in a reduction of fetal oxygenation which preceded other measures of fetal distress [1].

The present study demonstrates that maternal Sa_{O_2} values <90% occur commonly during normal labour in healthy women, but failed to show adverse effects on either the fetus or baby, when assessed by routine clinical methods. However, such methods are acknowledged to be relatively insensitive indicators of fetal well-being [1]. Cord blood gas analysis might be a better indicator and should form part of further studies.

No single cause of hypoxia is apparent from this study. In the second stage it occurred usually whilst the mother was pushing during contractions and is presumably a result of breath-holding. In the first stage it occurred commonly between contractions and was terminated by the onset of a further contraction.

Hyperventilation during contractions results in hypocapnia, which reduces ventilatory drive and leads to hypoxia from hypoventilation [1]. Pethidine may reduce hyperventilation during contractions and thus attenuate the hypocapnia. However, it may diminish the hypercapnic ventilatory drive and thus accentuate the effect of hypocapnia [2]. Nitrous oxide may contribute to hypoxia by reducing hypoxic ventilatory drive [3] and by inducing diffusion hypoxia [4]. All these factors could combine in the late first stage, when the most profound hypoxia was noted.

Many potential causes of hypoxia during labour are removed by effective extradural analgesia [5]. It prevents hyperventilation during contractions and removes the need for nitrous oxide or opioid analgesia.

We have shown that transient hypoxic episodes are common in healthy women during normal labour managed with pethidine and nitrous oxide and, in some women, profound hypoxia occurs which does not seem to be detected readily by the usual attendants. These episodes did not appear to affect fetal well-being. However, continuous pulse oximetry should be considered in high risk labours, such as mothers with pre-eclampsia, cardiac or respiratory disease or fetal intra-uterine growth retardation.

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INTERACTION OF KETAMINE WITH ATRACURIUM

P. TOFT AND S. HELBO-HANSEN

SUMMARY

The effect of ketamine on the duration of atracurium-induced neuromuscular blockade was studied in 40 healthy patients anaesthetized with midazolam, fentanyl and nitrous oxide. Twenty received, in addition, i.v. ketamine 2 mg kg^{-1} *followed by an infusion of 2 mg* kg^{-1} h^{-1}*. Atracurium 0.5 mg* kg^{-1} *was injected i.v. and the time to 25% recovery of the twitch height was measured. It was 8.0 min longer in the ketamine group (*$P < 0.005$*), with a 95% confidence interval of from 2.3 to 11.8 min.*

Johnston and colleagues [1] found that ketamine potentiates neuromuscular blockade produced by tubocurarine, but not that produced by pancuronium or suxamethonium. The present study was designed to determine the effect on the block produced by atracurium.

METHODS AND RESULTS

Forty-six ASA class I or II patients scheduled for gynaecological surgery were allocated at random to a ketamine or a control group, after local Ethics Committee approval and informed consent were received. Exclusion criteria included arterial hypertension, mental disturbance and diseases or drugs which might interfere with neuromuscular transmission.

The patients were premedicated with 50 mg of dixyrazine (a phenothiazine derivative), given by mouth the night before surgery.

Anaesthesia was induced with midazolam 0.2 mg kg^{-1}, fentanyl 7 μg kg^{-1} and atropine 0.5 mg i.v., and maintained with fentanyl and 66% nitrous oxide in oxygen.

The ulnar nerve was stimulated supramaximally at the wrist through surface electrodes, and the force of contraction of the adductor pollicis was recorded using a force-displacement transducer (TD 100, Biometer, Denmark), with a resting load of 200–300 g. The stimuli applied were square waves of 0.2 ms duration, at 0.1 Hz (Myotest, Biometer, Denmark). The output of the transducer was recorded on a Myograph 2000 (Biometer, Denmark). Following a period of at least 10 min to allow stabilization of the twitch response, the patients in the ketamine group received ketamine 2 mg kg^{-1} i.v. followed by an infusion of 2 mg kg^{-1} h^{-1}. Atracurium 0.5 mg kg^{-1} was injected i.v. 2 min after the ketamine bolus dose, and the duration of neuromuscular blockade was measured from the end of injection until the twitch height had recovered to 25% of the control twitch height obtained at the end of the stabilization period.

Ventilation was controlled at all times, and adjusted to maintain the end-tidal carbon dioxide partial pressure at 5.0–5.5 kPa (Normocap, Datex).

Systemic arterial pressure was recorded every 5 min and central (upper oesophagus) and peripheral (thenar eminence) temperatures were monitored continuously (TR 9, Ellab, Denmark).

Mann–Whitney *U* tests were used for statistical analysis between groups. Probability values <0.05 were considered statistically significant.

Three patients in each group were withdrawn from the study because of various technical problems during the period of stabilization of the twitch response. The remaining two groups of 20 patients were similar with respect to age, weight and height.

The median (and 1st and 3rd quartile) duration of neuromuscular blockade was 38.2 (34.3–45.3) min in the control group, and 46.2 (43.6–48.6) min in the ketamine group ($P < 0.005$) (fig. 1).

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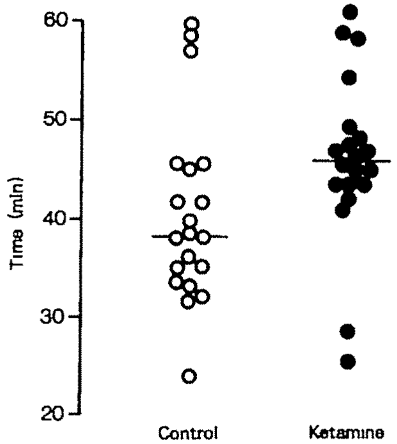

FIG. 1. Duration of neuromuscular blockade (time from end of injection of atracurium until 25% recovery of twitch height). Median values indicated by the horizontal lines ($P < 0.005$ between groups).

The 95% confidence interval was from 2.3 to 11.8 min.

There were no differences between the groups with respect to arterial pressures, and central and peripheral temperatures.

In the period between injection of atracurium and 25% recovery of the twitch response, eight patients in the control group and two patients in the ketamine group needed supplementary fentanyl 0.1–0.3 mg ($0.05 < P < 0.1$).

COMMENT

The present study demonstrates that, with midazolam, fentanyl and nitrous oxide as a basic anaesthetic, ketamine prolongs the duration of neuromuscular blockade induced by atracurium.

The results agree with *in vitro* studies on nerve-muscle and muscle preparations, which demonstrate that ketamine decreases the presynaptic release of acetylcholine [2] and reduces the sensitivity of the motor end-plate to acetylcholine [3]. Because of the large margin of safety of the neuromuscular transmission, ketamine has no demonstrable neuromuscular blocking effect of its own, but it causes an unexplained 2–10% increase in the evoked muscle twitch height [1,2,4,5].

Based on the *in vitro* studies [2,3], it is reasonable to expect that ketamine potentiates the effect of all neuromuscular blocking drugs, but results from *in vivo* studies are inconclusive. In one study, ketamine potentiated the effect of suxamethonium, but not that of pancuronium and tubocurarine [5], while in another, ketamine potentiated the effect of tubocurarine, but not those of pancuronium or suxamethonium [1].

The groups in the present study were comparable regarding central temperature, peripheral temperature and arterial pressure. There was a slight, but not statistically significant difference between the groups with respect to the supplementary dose of fentanyl. It is unlikely that this would affect the duration of neuromuscular blockade [6]. Because of the large individual variability in sensitivity to non-depolarizing neuromuscular blocking agents, the clinical implication of the 21% increase in the duration of neuromuscular blockade is limited, but does emphasize the need for more frequent use of monitoring of neuromuscular transmission. It remains to be established if ketamine affects the duration of neuromuscular blockade induced by other neuromuscular blocking drugs, and if it affects neuromuscular transmission when the margin of safety is otherwise reduced.

ACKNOWLEDGEMENTS

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CEREBRAL BLOOD FLOW DURING ANAESTHESIA: INFLUENCE OF PRETREATMENT WITH METOPROLOL OR CAPTOPRIL

K. JENSEN, L. BUNEMANN, S. RIISAGER AND L. J. THOMSEN

SUMMARY

We have studied the influence of a beta adrenergic blocking agent and an angiotensin converting enzyme (ACE)-inhibitor on cerebral blood flow (CBF) during general anaesthesia before surgery. Nine patients served as controls and received no special pretreatment. Two other groups were allocated randomly to receive either metoprolol 0.07 mg kg^{-1} i.v. (nine patients) at the time of induction or captopril 1 mg kg^{-1} by mouth (11 patients) 1.5 h before induction. There was no significant difference in CBF or CBF values corrected for changes in Pa_{CO_2} (CBF$_{corr.}$) between the metoprolol group and controls. In the group pretreated with captopril, CBF$_{corr.}$ values were significantly lower compared with the metoprolol group. Low CBF$_{corr.}$ in association with low mean arterial pressure was observed in two patients treated with captopril. These findings suggest that treatment with ACE-inhibitors should be discontinued before anaesthesia.

Beta-adrenergic blocking agents and ACE-inhibitors are used widely for treatment of cardiovascular disease and as adjuvants in induced hypotension during anaesthesia for some surgical procedures. We have therefore examined the effects on cerebral blood flow (CBF) of these drugs in combination with general anaesthesia.

METHODS AND RESULTS

Following approval by the Hospital Ethics Committee and informed consent, 29 ASA I patients (five female) were studied in the operating theatre before undergoing minor surgery under general anaesthesia. In all patients, CBF was measured before surgery, using an i.v. injection of xenon-133 into an arm vein. The emitted radiation was detected by a Novo Cerebrograph 10A. Recording of remaining activity in the brain was continued for 11 min.

In this study CBF was derived from the initial slope index and the CBF values were corrected for changes in arterial carbon dioxide tension (CBF$_{corr.}$) by a factor of 0.53% per kPa of Pa_{CO_2}.

Patients were allocated randomly to two groups: one group ($n = 9$) received metoprolol 0.07 mg kg^{-1} i.v. at induction of anaesthesia, the other group ($n = 11$) captopril 1 mg kg^{-1} by mouth together with premedication. These two groups were compared with a group of nine patients receiving no pretreatment. The three groups were comparable with respect to age (range 20–48 yr), bodyweight (range 55–98 kg) and resting arterial pressure (range 76–113 mm Hg).

All patients received identical anaesthetic techniques. Premedication was with morphine 10–15 mg and hyoscine 0.4–0.6 mg according to age and weight and induction was with thiopentone 4–6 mg kg^{-1} followed by tubocurarine 0.45–0.75 mg kg^{-1} with subsequent tracheal intubation. Anaesthesia was maintained with 0.8–1.0% enflurane and 66% nitrous oxide in oxygen, using intermittent positive pressure ventilation and a non-rebreathing system. Carbon dioxide concentrations were monitored continuously to ensure steady-state at the times of measurement.

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TABLE I. *Cerebral blood flow (CBF), cerebral blood flow corrected for changes in* Pa_{CO_2} *(*CBF_{corr}*) and mean arterial pressure (MAP) during general anaesthesia in patients with and without pretreatment with metoprolol or captopril (mean [range] (SD)) and paired comparison of the three groups by* t *test and Mann–Whitney test*

	Without (N) pretreatment ($n = 9$)	Captopril (C) pretreatment ($n = 9$)	Metoprolol (M) pretreatment ($n = 11$)
MAP (mm Hg)	81.11 [70–100] (11.94)	61.55 [53–77] (9.61)	67.78 [55–80] (9.18)
CBF (ml/100 g min^{-1})	48.22 [34.6–70.9] (4.95)	46.35 [29–71.7] (9.53)	55.30 [34.2–67.4] (7.47)
CBF_{corr} (ml/100 g min^{-1})	44.90 [39.4–53.2] (4.95)	38.79 [24.3–61.5] (9.53)	50.02 [37.4–58.8] (7.47)
Pco_2 (kPa)	5.49 [4.67–6.41] (0.595)	5.71 [4.54–6.60] (0.731)	5.58 [4.99–6.05] (0.324)
Statistical tests			
Variable	M–N	C–N	M–C
CBF	ns	ns	ns
CBF_{corr}	ns	ns	$P < 0.05$
MAP	$P < 0.05$	$P < 0.001$	ns
Pco_2	ns	ns	ns

CBF was measured 30 min after general anaesthesia had been established. At the time of CBF determinations, arterial blood samples were obtained for measurement of oxygen and carbon dioxide tensions (ABL 3—Radiometer).

Values for CBF, $CBF_{corr.}$ and mean arterial pressure (MAP) were analysed using Kruskal–Wallis and Mann–Whitney tests.

There was no significant variation in MAP in the patients pretreated with metoprolol compared with the patients pretreated with captopril. MAP in patients pretreated with either metoprolol or captopril was significantly lower than MAP in patients without pretreatment. There were small, insignificant, differences in Pa_{CO_2} between the groups, with slightly higher values in the captopril group.

In two patients pretreated with captopril we found low $CBF_{corr.}$ values (24.3 and 25.4 ml/100 g min^{-1}). MAP in both these patients was low also (53–54 mm Hg).

We found no significant differences in the measured CBF between the groups. There were significantly lower $CBF_{corr.}$ values in the group pretreated with captopril compared with those pretreated with metoprolol. There were no significant differences in CBF_{corr} values between the group pretreated with metoprolol and the group without pretreatment (table I).

COMMENT

Beta-blocking drugs and ACE-inhibitors are used widely in the treatment of arterial hypertension and cardiac disease. Both drugs are used as pretreatment for young patients undergoing surgery during controlled hypotension [1,2]. Beta-blocking drugs suppress the sympathetic adrenergic system and reduce liberation of renin from the juxtaglomerular cells [3]. ACE-inhibition reduces plasma concentrations of angiotensin II, increases parasympathetic tone, reduces plasma concentrations of aldosterone and decreases the breakdown of bradykinin [1,2].

Several studies in rats have shown that CBF is preserved during captopril induced hypotension [4,5]. A study of 22 patients receiving captopril and undergoing cardiac surgery led to the recommendation that captopril therapy should be maintained in the perioperative period [6].

In this study we observed significantly lower values of MAP in the two groups receiving therapy compared with the group without pretreatment. In the captopril group, CBF_{corr} was lower than in the other two groups, with a significant difference between captopril and metoprolol groups. We found low CBF_{corr} values in association with low MAP values in two patients; both received captopril.

There were no complications during anaesthesia associated with pretreatment with either group of drugs.

We suggest that discontinuing ACE-inhibitor treatment should be considered before anaesthesia, whilst therapy with beta-blocking drugs may be maintained.

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INFLUENCE OF SUXAMETHONIUM ON THE ACTION OF SUBSEQUENTLY ADMINISTERED VECURONIUM OR PANCURONIUM

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SUMMARY

The effects of suxamethonium were studied on the onset time and duration of action of vecuronium or pancuronium in 45 adult patients anaesthetized with halothane and nitrous oxide. After an intubating dose of suxamethonium, the force of the evoked twitch returned to a value greater than control. The onset of the reduction in force produced by subsequent administration of vecuronium or pancuronium was faster and recovery slower. This potentiating effect of suxamethonium persisted for at least 2 h.

Because of its rapid onset and short duration of action, suxamethonium is commonly used clinically to facilitate tracheal intubation. It is also common practice to follow a bolus injection of suxamethonium with a long-acting non-depolarizing neuromuscular blocking drug to maintain block during procedures of long duration. The interaction between suxamethonium and such subsequently administered agents has been documented frequently. However, no previous study has demonstrated if this interaction is clinically significant.

The present study was undertaken to determine the magnitude and duration of possible interactions between suxamethonium and subsequently administered non-depolarizing neuromuscular blocking drugs. Two steroids, vecuronium and pancuronium, were chosen—vecuronium for its reportedly unequivocal interaction with suxamethonium [1–4], and pancuronium, a bisquaternary analogue of vecuronium, because there is controversy regarding its interaction with suxamethonium [1,5–6].

METHODS AND RESULTS

The study was approved by the local Ethics Committee. Informed consent was obtained from 45 adult patients (ASA class I or II), aged 16–65 yr, none of whom was taking medication or suffering from an illness known to affect neuromuscular function. They were allocated randomly to group A (25 patients who received suxamethonium) or group B (20 patients of comparable age and weight who did not receive suxamethonium). All patients were premedicated with a combination of pethidine and atropine i.m. 1 h before induction of anaesthesia by inhalation of 2% inspired halothane and 50% nitrous oxide in oxygen. Ventilation was assisted by mask.

As soon as the patient became unconscious, the ulnar nerve was stimulated electrically with supramaximal stimuli of 0.2 ms duration at 0.1 Hz, via surface electrodes on the wrist. The force of adduction of the thumb was measured with an FT-611 transducer (Nihon Kohden Inc., Japan) and recorded continuously on an RM = 6000 polygraph system (Nihon Kohden Inc., Japan). Approximately 15 min after induction of anaesthesia, when a stable twitch tension was obtained, the trachea was intubated, either following suxamethonium 1 mg kg^{-1} i.v. (group A) or without this drug (group B). In group B, tracheal intubation was facilitated by tracheal administration of 4% lignocaine. Anaesthesia was maintained thereafter with nitrous oxide and 0.8–1%

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TABLE I. *Mean (SEM) onset time and duration of action of the intubating dose (0.08 mg kg^{-1}) and maintenance doses (0.02 mg kg^{-1}) of vecuronium or pancuronium with and without prior suxamethonium 1 mg kg^{-1}. Significantly different from values without suxamethonium (Student's* t *test):* $*P < 0.05$; $**P < 0.01$

	Onset time of intubating dose (min)	Clinical duration (min)			
		Intubating dose	Maintenance doses		
			1	2	3
Vecuronium	3.9 (0.3) ($n = 10$)	30.2 (0.3) ($n = 10$)	16.0 (0.8) ($n = 10$)	16.6 (1.4) ($n = 10$)	16.4 (0.9) ($n = 10$)
Suxamethonium + vecuronium	2.2 (0.1)** ($n = 10$)	36.1 (1.5)** ($n = 10$)	21.7 (0.7)** ($n = 10$)	22.9 (1.1)** ($n = 10$)	23.5 (1.2)** ($n = 9$)
Pancuronium	6.6 (0.8) ($n = 10$)	68.3 (6.4) ($n = 10$)	45.9 (4.1) ($n = 10$)	48.5 (3.3) ($n = 10$)	
Suxamethonium + pancuronium	1.7 (0.2)** ($n = 10$)	92.0 (6.8)* ($n = 10$)	60.9 (4.1)* ($n = 8$)	56.0 (2.6) ($n = 6$)	

inspired halothane, and ventilation was controlled to achieve normocapnia throughout the experiment. Rectal or oesophageal temperature was monitored and maintained at more than 35 °C.

After administration of suxamethonium, twitch tension returned to a level greater than control. In five patients in group A, the time course of change in the increased twitch tension was observed for 60 min. After complete recovery from suxamethonium-induced neuromuscular block in the remaining 20 patients in group A (19.6 (SEM 0.7) min after administration of suxamethonium), and after a comparable interval in group B, the patients received 0.08 mg kg^{-1} of either vecuronium or pancuronium and thereafter received, as maintenance doses, 0.02 mg kg^{-1} of the same drug each time the twitch tension recovered to 25 % of the control value before administration of suxamethonium. Onset time (time from injection to development of the maximal twitch depression) of the intubating dose and clinical duration (time from injection to recovery of the twitch tension to 25 % of control) of both the intubating dose and maintenance doses were noted for each patient. The changes in twitch tension after suxamethonium administration were tested for statistical significance compared with control using paired Student's t test. Comparisons of the changes in onset and recovery times between groups were by Student's t test. In both cases, $P < 0.05$ was considered significant.

After recovery from suxamethonium-induced neuromuscular block, mechanical twitch tension increased ($P < 0.01$) to 123.8 (2.5) % (mean (SEM); $n = 25$) of control. Twitch tension then decreased gradually, but remained increased (117.2 (2.7) %, $n = 5$) 60 min later. With prior administration of suxamethonium, the onset times of vecuronium and pancuronium were significantly shortened. The clinical durations were prolonged significantly except for that of the second maintenance dose of pancuronium (table I).

COMMENT

In common with previous studies [1,5–6], our data confirmed the potentiating effect of suxamethonium on the action of vecuronium administered subsequently. With prior administration of suxamethonium, the onset was accelerated and duration of action was prolonged significantly.

In contrast, controversy exists with regard to the effect on pancuronium. Katz [5] reported that the degree of partial neuromuscular block produced by a bolus injection of pancuronium 0.02 mg kg^{-1} was potentiated by prior administration of suxamethonium, while Krieg, Crul and Booij [1] found no potentiation with pancuronium 0.016 mg kg^{-1}. Walts and Rusin [6] reported that time for recovery from complete neuromuscular block produced by a bolus injection of pancuronium 0.05 mg kg^{-1} was not affected.

The difference between the previous results and ours may be explained as follows. First, the baseline of twitch depression changes after suxamethonium. It follows that the degree of neuromuscular block could be assessed differently according to the variation in control values. The varying results with pancuronium may be attributed, in part, to the difference in the control values chosen. Second, in view of the long-acting nature of pancuronium and the larger dose given in this study, it is conceivable that a minor shift in potency may be associated with a clinically significant change in duration of action. Third, the neuromuscular effects of halothane may have affected our results. Although end-tidal concentration of halothane was not monitored in this study, inspired concentration and duration of halothane administration were almost identical between patients with and without prior administration of suxamethonium. It is unlikely, therefore, that there was a significant difference between groups, throughout the study, in the blood concentration of halothane.

d'Hollander and colleagues [3] reported that the action of vecuronium was potentiated 45 min after recovery from suxamethonium-induced neuromuscular block. d'Hollander's group has also shown [4], that the potentiation of vecuronium was not obtained 90 min later. Our finding that suxamethonium failed to potentiate the second maintenance dose of pancuronium suggests that the effect persists at least 2 h, but not more than 3 h.

The clinical implications of this study are that the clinician should be aware of the fact that suxamethonium does potentiate vecuronium and pancuronium. Using a nerve stimulator will allow the effect in individual patients to be monitored and add to patient safety. In addition, it may be inappropriate to use suxamethonium when the neuromuscular effects of new drugs are studied.

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NATURAL KILLER CELL ACTIVITY IN A PATIENT UNDERGOING RESECTION OF PHAEOCHROMOCYTOMA

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Natural killer (NK) cells were discovered in the mid-1970s, because of their capacity to kill directly tumour cell lines, infected host cells and some normal cell types [1,2]. They are potentially important in protection against tumour cells and infections, and in immunoregulation, although their exact role *in vivo* remains to be clarified [3].

NK cell activity is depressed after major surgery, while a transient increase in activity has been demonstrated during the early stages of anaesthesia and surgical procedures [4–9]. The endocrine stress response to surgery seems to be important [9,10]. Serum cortisol and plasma adrenaline are prominent markers of this response and several studies have demonstrated that adrenaline enhances NK cell activity *in vitro* and *in vivo* [11–13], while corticosteroids inhibit activity [14,15].

Phaeochromocytoma is a rare tumour which secretes catecholamines, often in massive quantities. This report describes the relationship between plasma catecholamine concentrations and NK cell activity in a patient undergoing surgical removal of phaeochromocytoma.

CASE REPORT

The patient was an otherwise healthy 35-year-old woman (weight 68 kg) with a phaeochromocytoma demonstrated by angiography and hormone analysis. She was admitted to the intensive care unit on the day before operation. A central venous catheter, a lumbar extradural catheter and an arterial cannula were inserted using local analgesia, and arterial and central venous pressure and cardiographic monitoring were established.

The patient did not receive any preoperative α-blocking agents or other medication. No premedication was given, at the request of the patient. Three hours before operation, extradural analgesia was induced with 0.5% bupivacaine 5 ml every 10 min until analgesia, tested by pinprick, extended from S5 to T4 (a total of 25 ml of bupivacaine).

Anaesthesia was induced with fentanyl 0.3 mg and etomidate 26 mg, and neuromuscular block was achieved with pancuronium 8 mg. Anaesthesia was maintained with 0.5–2% isoflurane and 66% nitrous oxide in oxygen. Supplementary doses of fentanyl and pancuronium were given as needed. Extradural analgesia was maintained with incremental doses of 0.5% bupivacaine 5 ml every 1 h. The patient underwent mechanical ventilation using a Servo ventilator. At the end of operation, residual neuromuscular blockade was antagonized with neostigmine 2.5 mg preceded by atropine 1 mg.

The durations of anaesthesia and surgery were 160 min and 110 min, respectively. Hypertension with mean arterial pressure (MAP) up to 155 mm Hg occurred during tumour manipulation and removal, and was controlled with infusions of nitroglycerin and phentolamine. Hypotension

SUMMARY

This report describes the relationship between plasma catecholamine concentrations and natural killer (NK) cell activity in a patient undergoing surgical removal of a phaeochromocytoma. The findings confirm the role of adrenaline as a potent stimulator/inducer of NK cell cytotoxicity in vivo.

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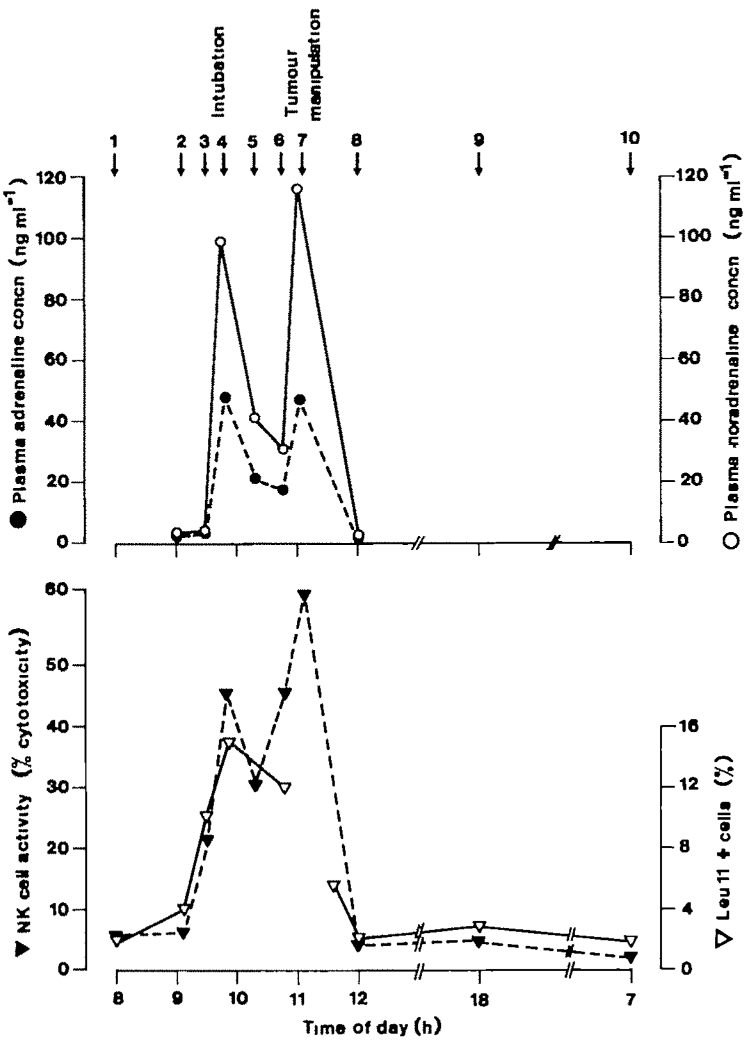

FIG. 1. NK cell activity, percentage of Leu 11+ cells, and plasma adrenaline and noradrenaline concentrations in a patient undergoing resection of phaeochromocytoma. Blood samples are indicated by arrows. Sample 1 = before operation and extradural analgesia; 2 = before induction of general anaesthesia; 3 = during general anaesthesia; 4 = immediately after tracheal intubation; 5 = just before skin incision; 6 = after skin incision; 7 = tumour manipulation and removal; 8 = completion of surgery; 9 = 6 h after skin suture; 10 = first day after operation.

(MAP 45 mm Hg) was noted just after the tumour was removed, and was treated with fluid infusions and dopamine. The postoperative course was uneventful.

Arterial blood was sampled for determination of NK cell cytotoxicity, distribution of Leu 11+ cells, and measurement of plasma adrenaline and noradrenaline concentrations as indicated in figure 1. Plasma catecholamine concentrations were measured by a single isotope-derivative assay [16].

NK cell cytotoxicity assay

Separation of mononuclear cells, cryopreservation, and determination of NK cell cytotoxicity were performed as described previously [5]. Briefly, mononuclear cells were isolated by Ficoll–Hypaque (Lymfoprep, Nyegaard & Co., Oslo) gradient centrifugation. The cells were cryopreserved and stored in liquid nitrogen until all specimens from the patient could be tested simultaneously against K562 target cells in a 6-h chromium-51 release assay. All assays were performed in duplicate at effector to target cells ratios of 50:1, 25:1 and 12.5:1; results represent the 50:1 ratio. NK cell activity was expressed as percentage cytotoxicity according to the expression: % cytotoxicity = [(cpm experimental release − cpm spontaneous release)/(cpm maximum release − cpm spontaneous release)] × 100, where cpm = counts $\min^{-1}$; spontaneous release = radioactivity released from target cells in the growth medium; maximum release = radioactivity generated when the target cells were frozen and thawed three times in distilled water. The spontaneous release was 15% of the maximum release.

Lymphocyte subpopulation (Leu 11+ cells)

The relative percentage of NK cells in peripheral blood mononuclear cells was estimated by the use of the monoclonal antibody Leu 11 (Becton Dickinson, California) reacting selectively with NK cells [8].

RESULTS

The changes in NK cell activity, percentage of Leu 11+ cells, and plasma catecholamine concentrations are shown in figure 1.

Intubation of the trachea and tumour manipulation were associated with rapid and marked increases in plasma adrenaline and noradrenaline concentrations and in NK cell activity. The percentage of Leu 11+ cells also increased after intubation. Too few cells were obtained to permit accurate enumeration of Leu 11+ cells during tumour manipulation.

DISCUSSION

Surgical manipulation and removal of phaeochromocytoma may provoke excessive release of catecholamines and, accordingly, would be expected to induce acute peroperative changes in NK cell activity.

This clinical report confirms the role of adrenaline as a potent stimulator/inducer of NK cell cytotoxicity *in vivo* [8,11,13]. Furthermore, the results suggest a positive correlation between NK cell activity and the number of circulating Leu 11+ cells. The increase in NK cell activity, at least after intubation of the trachea, may be explained by an increase in the number of circulating NK cells.

In a previous study of patients undergoing coronary artery bypass grafting, intubation of the trachea was not accompanied by an increase in plasma adrenaline or noradrenaline concentrations, but by a small but significant decrease [8]. Although plasma catecholamine concentrations increased markedly after intubation of the trachea in the present patient, no comparison is possible because of differences in the underlying diseases and anaesthetic techniques used.

All normal individuals have active NK cells, with the highest activity observed in blood and spleen. There are great interindividual variations in NK cell activity with low and high responders and also some linkage to certain MHC (major histocompatibility complex) haplotypes, sex, age, smoking, exercise and other systemic factors [17]. In the present patient NK cell activity was low both before and after operation.

In contrast with other cytotoxic cells, such as T-lymphocytes and monocytes, NK cells can be mobilized or activated within minutes. The NK cell system, therefore, together with the sympatho-adrenal system, may participate in the general pattern of reactions to stress and harmful or noxious stimuli. The NK cell system may thus rapidly enhance the defence of the organism against tumours and microorganisms.

The present case report has added further evidence to the concept that catecholamines acutely regulate NK cell activity during anaesthesia and surgery.

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ANAESTHETIC MANAGEMENT OF A PATIENT WITH FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

D. L. DRESNER AND H. H. ALI

SUMMARY

We describe the anaesthetic management of a patient with a rare form of muscular dystrophy (Facioscapulohumeral or Landouzy–Dejerine type). Anaesthesia and controlled ventilation using alfentanil–nitrous oxide and atracurium was satisfactory. In this patient, sensitivity to atracurium was found to be similar to that of the normal population, but more rapid recovery was observed.

The muscular dystrophies are a heterogeneous group of inherited myopathies. Clinical and genetic analysis allows classification into four general forms of the disease. In decreasing order of prevalence, these comprise Duchenne dystrophy, Myotonic dystrophy, Limb-Girdle dystrophy and Facioscapulohumeral dystrophy.

Facioscapulohumeral dystrophy was described first in 1886 by two French physicians, Landouzy and Dejerine [1]. Its incidence of 5 per million births is 1/10 that of the Limb-Girdle type and 1/50 that of the Duchenne type. Onset occurs in adolescence, as opposed to the Duchenne type which has an onset before the age of 5 yr. Usually, the shoulders are affected first, with inability or difficulty in raising the arms; this may distinguish it from the distal involvement of the hands or feet in the myotonic dystrophies or the pelvic predominance in the Duchenne or Limb-Girdle types. Pseudohypertrophy is not present as in the Duchenne dystrophy, but facial weakness is characteristic of the Facioscapulohumeral type. Fortunately, this condition progresses slowly and the cardiomyopathy and conduction defects characteristic of the myotonic or Duchenne types have not been described. To our knowledge, there has been no report describing the anaesthetic management and, in particular, the response of a patient with Facioscapulohumeral dystrophy to atracurium neuromuscular blockade.

CASE REPORT

A 23-yr-old male presented for a right Steindler Flexorplasty. He presented with a diagnosis of Facioscapulohumeral dystrophy, and was the second generation of his family affected. The patient presented originally at age 16 yr with difficulty in arm movement. Electromyogram and nerve conduction velocity studies were consistent with his diagnosis and right deltoid muscle biopsy also was suggestive of muscular dystrophy. Physical examination revealed obvious atrophy of the shoulder girdle with marked winging of the scapulae. Proximal arms appeared wasted (fig. 1), compared with the relative normal appearance of the distal forearms and hands. The patient was unable to raise his arms and he required one arm to support the other for various manoeuvres. In addition, he showed clinical evidence of weakness of the forearm and hand muscles. No scoliosis was noted. Cranial nerves appeared normal, but the eyelids were opened easily from a weak squint. Deep tendon reflexes were diminished in the upper extremities. Gait was unaffected, but the patient was beginning to experience weakness of the tibial and peroneal muscle groups which required the use of a cane for support.

Vital signs were normal. Laboratory values included haematocrit 43%, creatine phosphokinase (CPK) 137 u. litre^{-1} (normal range 17–148) and lactate dehydrogenase (LDH) of 72 u. litre^{-1} (normal range 45–90) (the last two values are from a hospital assay referenced at 30 °C; the hospital has since converted to the standard 37 °C refer-

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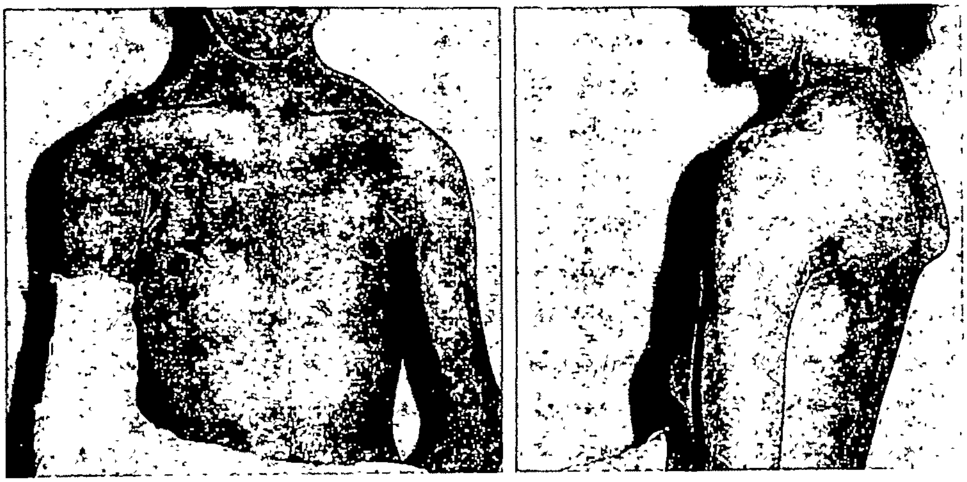

FIG. 1. Anterior view shows wasting of the sternocleidomastoid, infraclavicular, deltoid and other upper arm muscles. Lateral view shows significant winging of the scapulae.

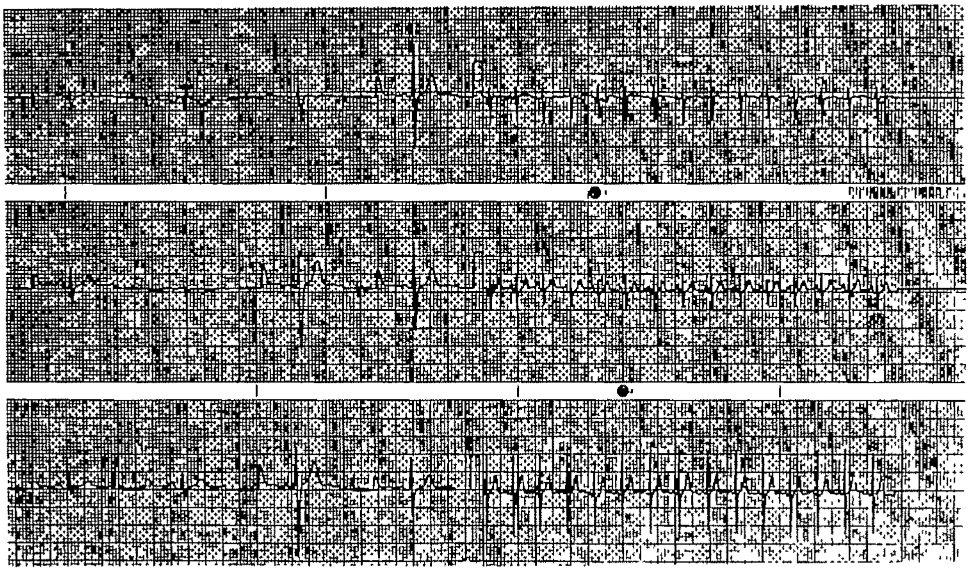

FIG. 2. Electrocardiogram. For description, refer to text.

ence). Chest x-ray was normal. Electrocardiogram (ECG) demonstrated normal sinus rhythm at 89 beat min^{-1} with marked right axis deviation (132°) and a tall R wave in lead V1 (fig. 2). Pulmonary function testing was consistent with an early restrictive defect. Lung volumes were studied by plethysmography which showed a residual volume of 1.09 litre (64 % of predicted).

Following written informed consent for the study and photography, the patient was premedicated with diazepam and morphine 1 h before surgery. After insertion of an i.v. cannula and attachment of ECG leads, sphygmomanometer cuff, pulse oximeter probe and apparatus for ulnar nerve stimulation and measurement of adductor pollicis tension [2], anaesthesia was induced with two consecutive boluses of alfentanil 25 $\mu g\ kg^{-1}$, followed by thiopentone 300 mg and the lungs were ventilated with 60 % nitrous oxide in oxygen. Evoked thumb adduction was monitored using a Grass FT-10 force transducer in response to supramaximal ulnar nerve stimulation at 0.15 Hz using two 23-gauge steel needle electrodes at the wrist [2].

After a stable control twitch response was obtained, atracurium was administered in increments of 50 μg kg^{-1} every 2 min. At a cumulative dose of 300 μg kg^{-1}, the twitch was depressed to approximately 5 % of control height. Tracheal intubation was accomplished easily. Anaesthesia was maintained with 66 % nitrous oxide in oxygen and an infusion of alfentanil 1 μg kg^{-1} min^{-1}. A stethoscope and temperature probe were inserted into the oesophagus, and the temperature was maintained at 36.5 °C. The evoked single twitch response was allowed to recover spontaneously to control height and the train-of-four (TOF) ratio to greater than 90 %. The 5–95 % and the 25–75 % single twitch recovery times were 21.5 and 9.0 min, respectively (fig. 3A). Following complete recovery, another bolus dose of atracurium 200 μg kg^{-1} was administered. This dose resulted in complete ablation of the single twitch. Spontaneous recovery was followed until the single twitch recovered to control height and the TOF ratio exceeded 80 % (fig. 3B). The 5–95 % single twitch recovery time following the single bolus dose 16.5 min and the recovery index (25–75 % recovery) was 6.5 min.

No anticholinesterase agent was used. The 2-h procedure was uneventful. Emergence was rapid following discontinuation of the alfentanil infusion and nitrous oxide; the patient awakened, was responsive and was transferred to the recovery room. Postoperative follow-up on the ward demonstrated no anaesthetic-related complications. There was neither recall of intraoperative events, nor immediate postoperative discomfort. The patient related no complaints of perioperative ventilatory difficulty or muscle weakness.

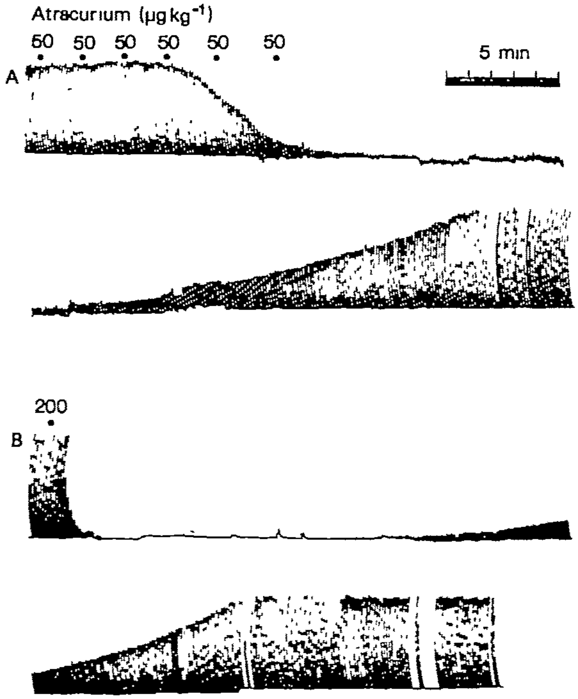

FIG. 3. Evoked thumb adduction in response to 0.15-Hz single twitch ulnar nerve stimuli. A: Increments of atracurium 50 μg kg^{-1} to approximately 95 % twitch depression and spontaneous recovery to control twitch height. B: Following complete recovery of the twitch in A, the response to a single bolus of atracurium 200 μg kg^{-1} at the mark and spontaneous recovery of the twitch to control height with a train-of-four ratio of 80 %.

DISCUSSION

The muscular dystrophies are characterized clinically by progressive weakness and histologically by degeneration and regeneration of muscle or tissue reaction to these processes. In this group of disorders, complications include pulmonary dysfunction, muscle contracture, kyphoscoliosis, cardiac abnormalities and susceptibility to malignant hyperthermia, although not all of these problems present in each of the various dystrophies. In general, the anaesthetic implications in such patients include failure of ventilation, cardiac dysfunction, arrhythmias, sudden death, hyperkalaemia, malignant hyperthermia and abnormal response to halothane or depolarizing neuromuscular blockers with muscle contracture, rhabdomyolysis, myoglobinuria and renal failure [3–10].

Facioscapulohumeral muscular dystrophy is the least prevalent of all the known inherited myopathies. It has not been shown that this type of muscular dystrophy is associated with problems such as cardiomyopathy, arrhythmias and conduction defects which are present in the Duchenne pseudohypertrophic type which primarily affects the pelvic girdle and calf muscles, or Steinert's myotonia dystrophica with which it shares the facial and neck muscle weakness. Although our patient presented some evidence of early mild restrictive pulmonary defect and an ECG consistent with right ventricular hypertrophy, no intraoperative or perioperative problems developed. This patient's disease was slowly progressive, and appears to have started to affect the pelvic and lower limb muscles. His muscle enzymes studies were within normal limits, although 1 year previously he was reported to have a moderately increased CPK value.

The striking feature in this patient was his response to atracurium. He appeared to have sensitivity to this non-depolarizing agent similar to that of the normal population, but recovery was much faster, especially following the second bolus dose, with 5–95% and 25–75% single twitch recovery times of 16.5 and 6.5 min, respectively, compared with 28.8 (SEM 2.5) and 12.3 (0.7) min, respectively, in the normal patient [11].

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COMPLICATIONS OF SPINAL ANAESTHESIA FOLLOWING EXTRADURAL BLOCK FOR CAESAREAN SECTION

P. A. STONE, J. THORBURN AND K. S. R. LAMB

SUMMARY

After extradural blockade failed to extend sufficiently for elective Caesarean section, spinal anaesthesia was performed using 1.6 ml of hyperbaric 0.5% bupivacaine solution in 8% glucose (Marcain Heavy). The patient rapidly developed sensory blockade to the level of T2, and became distressed and dyspnoeic. General anaesthesia was induced. Despite i.v. ephedrine and fluid loading, severe hypotension occurred, which responded subsequently to further doses of ephedrine and infusion of colloid. A healthy infant was delivered by Caesarean section.

Spinal anaesthesia is unpredictable in obstetric practice [1, 2]. Cases of unexpectedly high blockade, including total spinal block, are reported in obstetric patients. Russell [3] described inadvertent total spinal blockade for Caesarean section in a patient who received a dose of 0.75% bupivacaine 2.0 ml. Stonham and Moss [4] reported a total spinal using 3.0 ml and two high blocks (T1) using 0.5% bupivacaine 2.0 and 3.0 ml. In Russell and Holmqvist's series of 40 patients [2] receiving 2.5 ml of either hyperbaric or plain 0.5% bupivacaine, no ventilatory difficulty was experienced, although a number of high blocks occurred.

This case report describes a rapid onset of high spinal blockade following only 1.6 ml of hyperbaric 0.5% bupivacaine solution in 8% glucose, (Marcain Heavy) in a patient in whom extradural blockade had failed.

CASE REPORT

A 24-yr-old patient (weight 54 kg, height 153 cm) was admitted for elective Caesarean section at 38 weeks gestation. The patient had undergone previous Caesarean section under general anaesthesia and she requested to be awake for this delivery.

One litre of Ringer–lactate solution was infused i.v. and, with the patient sitting, the extradural space was identified by loss of resistance to air, using a 16-gauge Tuohy needle at L3–4. Loss of resistance occurred at 4 cm and an extradural catheter was inserted 4 cm into the space.

A test dose of 0.5% bupivacaine solution (Marcain) 3 ml was injected via the catheter. Sequential doses of 0.5% bupivacaine were administered over the next 1 h: 10 ml at 5 min, 5 ml at 10 min and 8 ml at 30 min. As blockade was developing preferentially on the right, the catheter was withdrawn by 1 cm before further injection. At 45 min, 4 ml and at 55 min 3 ml were injected with the patient in the left lateral position. At 80 min the sensory block, identified by loss of sensation to pin-prick, extended from T6 on the right, and from T10 on the left with extension to sacral segments bilaterally. A total of 33 ml of 0.5% bupivacaine had been administered. At 75 min hypotension to 85/45 mm Hg was treated with ephedrine 6 mg i.v. with the patient in the left lateral position, which restored systolic arterial pressure to more than 100 mm Hg. The extradural block remained inadequate for Caesarean section. The patient still expressed a strong desire to remain awake for operation and it was decided to proceed to spinal anaesthesia.

The patient was transferred to theatre and the extradural catheter was removed. Arterial pressure was 105/70 mm Hg. After further i.v. fluid pre-load to a total volume of 2100 ml, subarachnoid block was performed at 2 h with the patient in the left-lateral position, using a 25-

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gauge spinal needle. Hyperbaric 0.5% bupivacaine 1.6 ml was given without barbotage. After approximately 30 s the patient was returned to the left-lateral tilt position. Within 3 min the sensory block had extended bilaterally to T4, and arterial pressure remained at 100/60 mm Hg. Slight head-up tilt was applied in an attempt to minimize further extension of the rapidly advancing block. The sensory block rose to T2 and the patient complained of difficulty in breathing. She was able to speak and cough, but was distressed by dyspnoea. Oxygen was supplied via a face-mask and Magill circuit. Good colour and tidal volume were maintained. There was no gross evidence of motor blockade in the upper limbs at that time, although circumstances did not allow detailed neurological examination.

In view of the patient's extreme distress, general anaesthesia was induced at approximately 2 h 10 min following 0.3 mol litre^{-1} sodium citrate 30 ml by mouth and pre-oxygenation. The table was levelled and left-lateral tilt maintained. Pre-induction arterial pressure was 95/45 mm Hg. A rapid-sequence induction with cricoid pressure was carried out with thiopentone 250 mg and suxamethonium 100 mg, and ephedrine 6 mg was given i.v. The trachea was intubated and intermittent positive pressure ventilation initiated. Anaesthesia was maintained with 0.4–0.6% enflurane and 50% nitrous oxide in oxygen. Shortly after induction, arterial pressure was 60/50 mm Hg and a further 6 mg of ephedrine was given i.v. and plasma protein solution infused. Systolic arterial pressure increased rapidly to 90 mm Hg and to 110 mm Hg within 5 min. Vasodilatation was noted in both upper and lower limbs. No further doses of neuromuscular blocker were required.

A male infant was delivered shortly after induction, with Apgar scores of 8 at 1 min and 9 at 5 min. By the end of surgery the total volume of i.v. fluid infused was 3200 ml, including 1200 ml of plasma protein solution. Estimated blood loss was 500 ml. Following recovery, the patient awoke and maintained adequate spontaneous ventilation via the tracheal tube. The patient was reassured, and the level of the sensory block was noted to be T2. Good grip strength and normal sensation were present in both hands. The trachea was extubated at 2 h 50 min and the motor and sensory block regressed gradually over the following 3 h.

DISCUSSION

In this patient, the decision to proceed to general anaesthesia was based on dyspnoea causing maternal distress, coincident with a rapidly advancing spinal block. The rapid sequence induction and intermittent positive pressure ventilation may have exacerbated the degree of hypotension.

An unacceptably high spinal block developed rapidly, but the maximum height is unknown because of general anaesthesia. In addition to rapidly advancing sensory block, other features indicative of a high block, including lack of requirement for depolarizing neuromuscular blockade, severe hypotension and profound dyspnoea. Fluid in a volume equivalent to 30% of the blood volume was infused before the spinal injection. There was no clinical evidence of pulmonary oedema at any time and by the end of general anaesthesia a further 1100 ml had been infused and the patient was not dyspnoeic on waking.

There are several possible mechanisms whereby such a high block may have resulted from such a low volume of local anaesthetic injected into the subarachnoid space. Compression of the space by extradural distension with 33 ml of solution, in addition to air, could be considerable in a patient 153 cm in height. Following a similar volume of extradural injection, Dennison [5] attributed failure of spinal anaesthesia to virtual collapse of the subarachnoid space. If collapse does occur it follows that a given dose of local anaesthetic within the space may be distributed more widely. In addition, the volume of cerebrospinal fluid decreases in late pregnancy and this is said to increase cephalad spread of subarachnoid local anaesthetic solution [6].

Another mechanism of widespread block is transfer of extradurally injected solution through the dural puncture. Hodgkinson [7] described three patients who developed a total spinal block in a study of 31 obstetric patients in whom successful extradural analgesia was administered following accidental dural puncture. The dural puncture would have been considerably larger in these patients than in ours. However, the volume of solution in the extradural space was considerable in our patient. In descriptions of the combined subarachnoid–extradural techniques [8,9] subarachnoid effects from the extradural drugs were not observed, but large volumes of extradural solution were not required.

This case demonstrates hazards from the use of multiple anaesthetic techniques in an obstetric patient. An extensive search of the recent literature has revealed no reference to the suggested doses for, or the effects of, spinal anaesthesia in the presence of established but inadequate extradural blockade.

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BILATERAL PNEUMOTHORAX FOLLOWING TRACHEAL INTUBATION

C. BISWAS, N. JANA AND S. MAITRA

SUMMARY

An elderly patient undergoing elective cholecystectomy, developed bilateral pneumothorax following intubation of the trachea and manual ventilation of the lungs. Diagnosis was confirmed by chest x-ray and drainage with wide bore cannulae. Drainage of the chest was necessary.

CASE REPORT

A 65-yr-old woman weighing 60 kg was admitted to RG Kar Medical College and Hospital, Calcutta, for elective cholecystectomy. Preoperative assessment showed that the patient was otherwise healthy. Heart rate was 80 beat min^{-1} and regular, arterial pressure 125/80 mm Hg and rate of ventilation 14 b.p.m. Examination of heart and lungs showed no abnormality and the patient's past medical history did not indicate any respiratory disease. Preoperative investigation revealed normal haematology and biochemical values and the electrocardiogram and chest x-ray did not show any abnormality.

On the night before the operation, the patient was given diazepam 10 mg by mouth to allay anxiety. Premedication was with pethidine 50 mg and trimeprazine 25 mg i.m 1 h before operation.

After pre-oxygenation for 5 min, anaesthesia was induced with thiopentone 3.5 mg kg^{-1}. Gallamine 2 mg kg^{-1} was given and tracheal intubation was performed under direct vision using a size 8 red rubber tracheal tube. Following intubation of the trachea, the lungs were ventilated manually with nitrous oxide 5 litre min^{-1} and oxygen 3 litre min^{-1} using a circle system. On auscultation of the lung fields, breath sounds were audible only at the apical regions. Approximately 2 min later, the patient developed cyanosis. Surgical emphysema began to develop on both sides of the neck, chest, abdomen and inguinal regions. Percussion of the chest revealed bilateral hyperresonance.

The operation was cancelled. Neostigmine 2.5 mg and atropine 1.2 mg were given i.v. to antagonize neuromuscular block and the lungs were ventilated with 100% oxygen. Shallow spontaneous ventilation was established quickly, but the patient remained cyanosed, even though she was breathing 100% oxygen. Cardiac arrest occurred 2 min later. Immediate external cardiac massage was applied and the patient was resuscitated successfully. Sodium bicarbonate 50 mmol $litre^{-1}$ was given i.v. with hydrocortisone 200 mg. Facilities were not available for analysis of arterial blood, but chest x-ray was performed and showed bilateral collapse of the lungs with massive bilateral pneumothoraces (fig. 1).

The diagnosis was confirmed by bilateral insertion of catheters into the pleural cavities. The catheters were connected to closed tube drainage systems and within minutes both lungs expanded and breath sounds were heard on auscultation. A repeated chest x-ray showed expansion of both lungs. The patient's condition improved dramatically and she was able to remove her tracheal tube. She was transferred to the postoperative ward for routine observation. Chest x-ray was repeated 6 h later and expansion of both lungs was confirmed (fig. 2).

The surgical emphysema resolved gradually and the chest drains were removed after 72 h. Chest x-ray was satisfactory. The patient was discharged from hospital 7 days later. She re-

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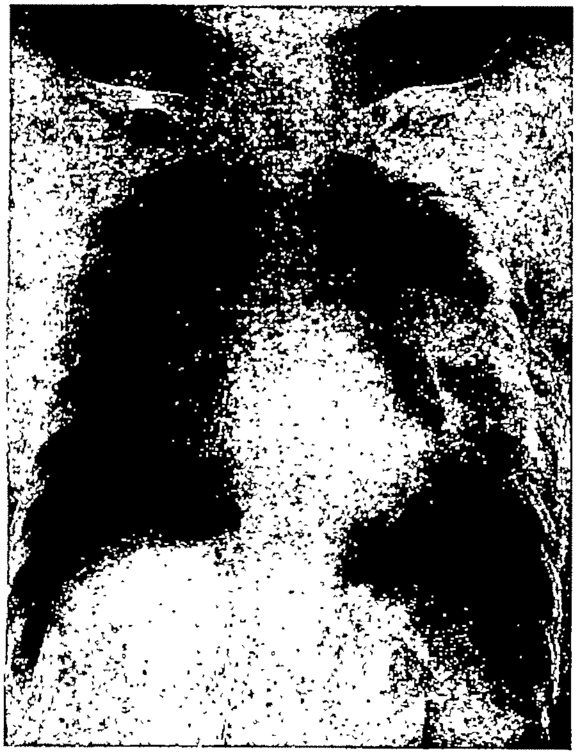

FIG. 1. First chest x-ray, showing bilateral pneumothorax.

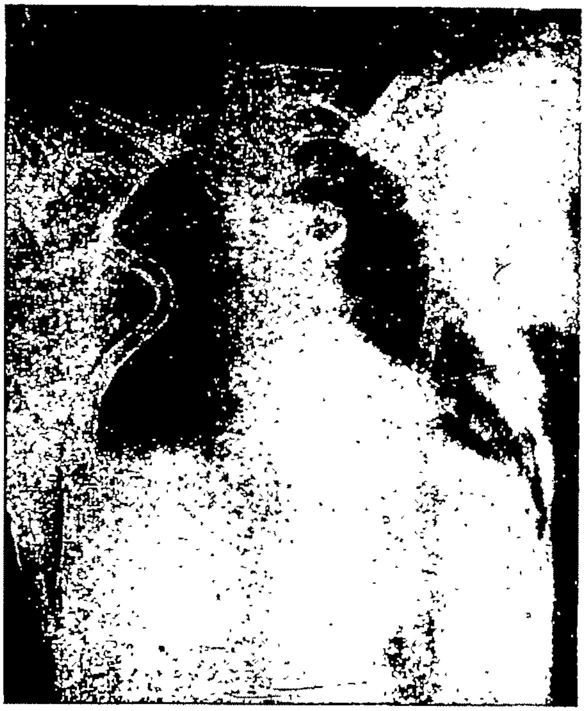

FIG. 2. Repeat chest x-ray following insertion of bilateral chest drains with lung expansion

turned to the hospital for chest x-rays at monthly intervals for 2 months. Her condition remained satisfactory and no other problems were found.

DISCUSSION

Bilateral pneumothorax following tracheal intubation and manual ventilation of the lungs in an otherwise healthy patient is extremely rare. Spontaneous pneumothorax may occur in any age group, but is found commonly between 15 and 35 years of age and is commoner in males than females. Approximately 30 % of the patients with spontaneous pneumothorax have chronic lung disease, especially bronchitis and emphysema. Traumatic pneumothorax is found in healthy individuals involved commonly in road traffic accidents and is associated usually with other injuries.

In our patient none of these factors existed and a diagnosis of iatrogenic pneumothorax was made therefore. Ideally, one should monitor the airway pressure throughout IPPV, but the incident happened where there was little monitoring available in our institution.

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EVALUATION OF THE AMBU CPAP SYSTEM

P. J. H. VENN

SUMMARY

We have assessed a Venturi driven device for delivering continuous positive airway pressure (CPAP) using a reservoir bag and expiratory valve under conditions of continuous flow and simulated spontaneous breathing. The system performed well and was economical, consuming only 3.5 litre min^{-1} of fresh gas. One Venturi was partially blocked and performed inadequately, but the function of a second one was close to the manufacturer's specification (inspired oxygen 33%, flow 20 litre min^{-1} against end-expiratory pressures of 0–1.8 kPa). Compliance curves for two reservoir bags (new and old) were defined; these showed that compliance increased as the pressure in the circuit increased. The characteristics of the expiratory valve approached those of a threshold resistor. Small fluctuations in airway pressure occurred at all settings of CPAP and decreased with the increasing compliance of the circuit at higher values of CPAP. The method provided to monitor the airway pressure was inaccurate and overestimated the true pressure by 20% at pressures greater than 1 kPa.

Continuous positive airways pressure (CPAP) is an established technique for improving arterial oxygenation when there is a mismatch of pulmonary ventilation and perfusion. This benefit is achieved largely by an increase in funtional residual capacity (FRC) [1–3]. However, there is recent evidence to suggest that patients with ventilatory failure may benefit from the decrease in inspiratory work associated with the use of CPAP [1,4–6], and that CPAP may be a more physiological form of management than mechanical ventilation [1,7]. In patients with respiratory failure, atelectasis may reduce FRC, thereby decreasing compliance. Restoration of FRC towards normal increases compliance and decreases airways resistance and inspiratory work [6]. In order to keep the work of ventilation to a minimum, little or no variation in airway pressure should occur during breathing [1,5]. This is best achieved with a high gas flow in the patient circuit [8], or by using a lower flow with a weighted bellows or a large volume–high compliance reservoir bag [9–11]. These maintain the pressure in the system by buffering the changes in flow during inspiration and expiration.

DESCRIPTION OF APPARATUS

Ambu International Ltd of Denmark has introduced a system combining the advantages of a high flow in the patient circuit with a low consumption of fresh oxygen (fig. 1). The gas flow is achieved by a Venturi driven by oxygen at a pressure of 3–4 bar, entraining air into a large (5-litre) compliant reservoir bag. This mixture may be enriched further by additional oxygen through an inlet on the bag mount. The gas mixture passes through a 1-m length of disposable corrugated tubing (and humidifier if desired) to a patient Y-piece. The expiratory limb of the Y-piece is connected to an adjustable spring loaded valve which provides the pressure difference between the circuit and the atmosphere. The valve consists of a circular plate pressed against a plastic seating by two springs. The mechanism is encased in a plastic housing. The pressure of gas in the system lifts the plate against the springs and allows gas to escape through the orifice. As the flow across the valve increases, the orifice increases also so that a relatively constant pressure is maintained in the circuit. In the steady state the pressure created by the compliance of the bag is sufficient to drive gas

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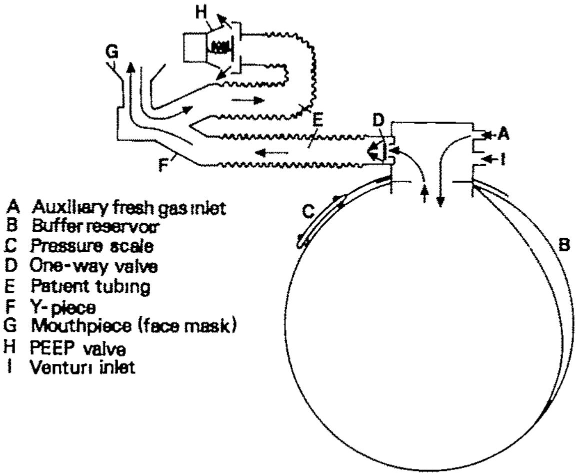

FIG. 1. Diagram showing the general arrangement of the Ambu CPAP system.

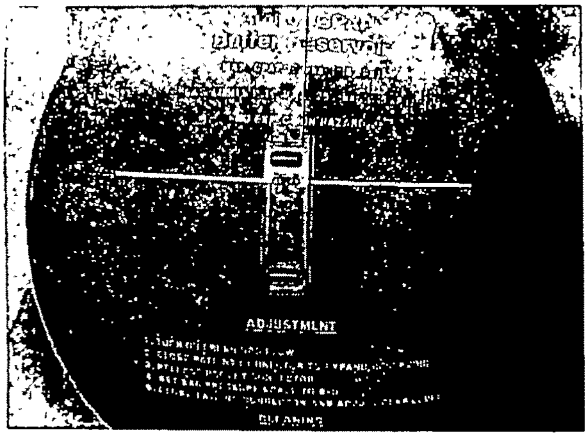

FIG. 2. The Ambu CPAP buffer reservoir bag showing the transparent strap provided to measure the pressure.

at 20 litre min^{-1} across the valve to atmosphere. The CPAP is gauged by measuring the distension of the bag using a transparent strap with a graduated scale of numbers which hangs in front of a single horizontal line drawn on the bag (fig. 2).

The manufacturers state that the system supplies fresh gas at a flow of 20 litre min^{-1} to the patient circuit. It is capable of delivering CPAP between 0 and 1.8 kPa, with an $F\text{I}_{\text{O}_2}$ of 0.33 (when the Venturi is driven by oxygen but with no auxiliary oxygen). The airway pressure should vary less than 0.2 kPa during quiet breathing. The Venturi consumes oxygen at 3.5 litre min^{-1}.

The instructions for use indicate that the system, with the exception of the Venturi and reservoir bag, can be cleaned by any conventional heat, chemical or gas sterilizing method. The reservoir bag should not be autoclaved, and the Venturi does not require cleaning.

MATERIALS AND METHODS

The Venturi, reservoir bag and expiratory valve were studied separately.

Analysis of the Venturi entrainment system

The device was assessed to see how the amount of CPAP would affect the total gas flow delivered to the patient circuit. The Venturi was connected to the hospital oxygen pipeline system at 4 bar. The patient Y-piece was replaced by a connection with a side arm attached to a spirit-filled manometer calibrated in mbar (0.1 kPa). Because of the difficulty in collecting gas issuing from the CPAP valve, the valve was replaced by a length of silastic tubing with an adjustable gate-clip. This was connected to a dry gas meter (Singer DTM-115) to measure the total flow through the system at ambient pressure. The time for 100 litres of gas to pass at constant flow through the system at pressures of 0–1.8 kPa was recorded and the flows expressed in litre min^{-1}. At each value of CPAP three flow measurements were made; in addition, the mean concentration of oxygen was calculated from three gas samples which were withdrawn from the system into a 100-ml oiled ground-glass syringe and analysed using a paramagnetic oxygen analyser (Servomex OA 101 MkII).

Analysis of the compliance characteristics of the reservoir bag and system

To investigate the compliance characteristics of the whole system, the pressure in the system was measured with the manometer as 100-ml increments of air were added from the ground-glass syringe through a three-way tap. The Y-piece in the patient circuit, the additional oxygen inlet to the bag and the CPAP valve at the end of the expiratory limb were sealed with rubber bungs (fig. 3). There is a one-way valve at the outlet from the bag mount directed into the patient circuit which prevents free communication between all parts of the system; this outlet was also sealed with a bung and the circuit connected to the bag mount via the Venturi inlet port and a double side arm for the attachment of the syringe and manometer. The whole system was tested for

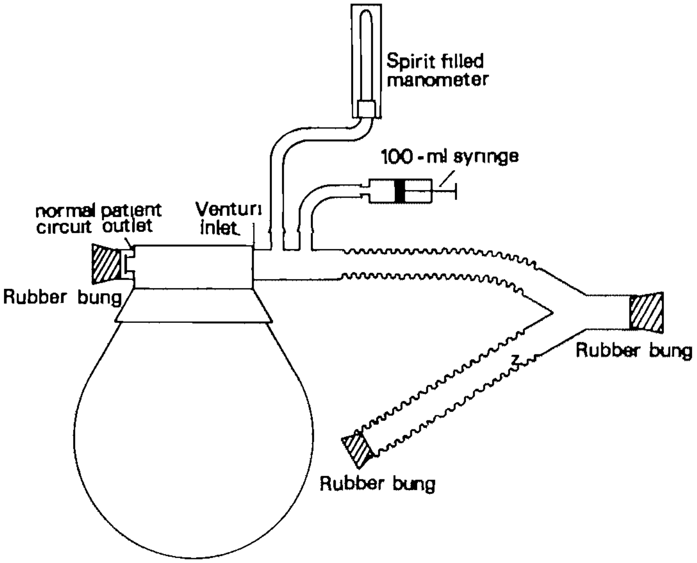

FIG. 3. Diagram showing the method used to measure the compliance of the reservoir bag and system (see text).

leaks using soap solution before the pressure measurements were made. To see if the compliance of the bag changed with age and use, a new bag and a bag which had been pressurized during use for several hours were tested. The reading taken from the transparent strap on the side of the bag was compared with the manometer pressure.

Analysis of the Ambu CPAP valve

The pressure across the valve was measured at different flows to see whether the valve functioned as a flow or as a threshold resistor. The manometer and CPAP valve were placed in series with a calibrated flow meter delivering air up to 100 litre min^{-1}. The valve was adjusted to give a pressure of 0.5 kPa at 20 litre min^{-1} flow and at that setting a series of pressure measurements was made as the flow was increased from 10 to 70 litre min^{-1} in 10-litre min^{-1} steps. Another set of readings was taken as the flow was reduced in stepwise fashion from 70 to 10 litre min^{-1}. The process was repeated for pressure settings of 1.0, 1.5 and 2.0 kPa.

In addition, measurements were made to demonstrate the effect of gravity on the characteristics of the valve. First, the valve was set to give a pressure of 1.0 kPa at a flow of 20 litre min^{-1} whilst held with its axis horizontal. The pressures were measured as the flow was changed stepwise between 10 and 70 litre min^{-1} as above, but with the distal end of the valve pointing upwards, horizontally or downwards.

Pressure variation during the ventilatory cycle

In order to examine the pressure fluctuations which occur whilst breathing at different values of CPAP, the system was connected to a lung model which simulates spontaneous ventilation. Flow, tidal volume and pressure in the bag and at the Y-piece were measured during the ventilatory cycle. A mechanically operated lung simulator was constructed to ensure a similar pattern of inspiratory and expiratory flow at all values of CPAP. It consisted of a pair of spring loaded bellows mounted in parallel on a rigid frame, and therefore linked mechanically. One bellows was driven by a ventilator (Penlon Nuffield Series 200), whilst the other bellows acted as the lung model for spontaneous ventilation. A resistance of 2.0 kPa litre^{-1} s^{-1} was placed in series with the lung bellows (fig. 4). A flow approximating to a square wave was generated during inspiration, with a decreasing flow in expiration. The Y-piece of the CPAP circuit was attached to the lung model through a Fleisch No. 1 pneumotachograph and the pressure across it was measured with a differential pressure transducer (Validyne) to derive flow. Electrical integration of the flow signal (Morgan Respiration Integrator Mk11) gave tidal volume. The pressure in the circuit was

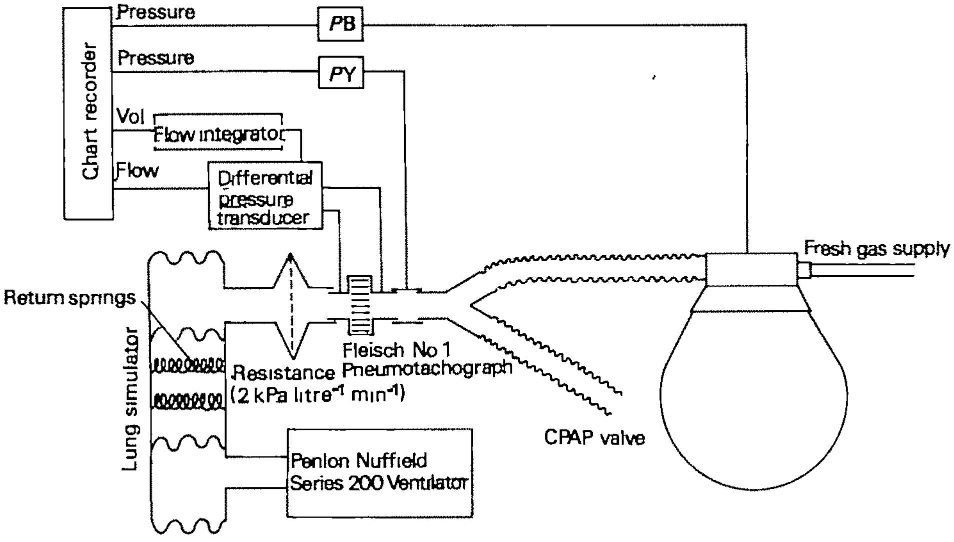
Chart recorder
Pressure
Pressure
Vol
Flow
PB
PY
Flow integrator
Differential pressure transducer
Fresh gas supply
Return springs
Lung simulator
Fleisch No 1 Pneumotachograph
Resistance (2 kPa litre⁻¹ min⁻¹)
CPAP valve
Penlon Nuffield Series 200 Ventilator

FIG. 4. Flow diagram showing how the system was connected to the simulated lung and monitoring (see text).

measured with a pressure transducer (Gould) connected between the Y-piece and the pneumotachograph, whilst the pressure in the bag was measured simultaneously through the auxiliary fresh gas port. The four signals were displayed on a chart recorder (Electromed MX19).

Calibration of the pressure and volume signals was carried out with the manometer and a 1-litre syringe, and the flow signal was calibrated with air from a flowmeter. The lung simulator was adjusted to give tidal volumes of 500 ml at a rate of 12 b.p.m. with an inspiratory:expiratory time ratio of 1:2. Inspiratory flow was approximately 15 litre min^{-1} with a peak expiratory flow of approximately 40 litre min^{-1} increasing to 50 litre min^{-1} at greater values of CPAP as the bellows compliance decreased. At each 0.2-kPa increment between 0 and 1.6 kPa, the CPAP valve was adjusted to give the required airway pressure at a constant flow with the lung simulator "switched off". During simulated spontaneous breathing, recordings were made of the fluctuation of pressure in the bag and at the Y-piece, with the flow and volume changes.

RESULTS

Characteristics of the Venturi and bag

The first Venturi studied (A) delivered a lower than expected flow, because of a partial blockage in the jet. A second Venturi (B) was tested subsequently. When CPAP was increased from 0 to 1.8 kPa using Venturi A, there was a mean reduction of gas flow through the patient circuit of 7.20 litre min^{-1} (from 18.69 litre min^{-1} to 11.49 litre min^{-1}) and the inspired oxygen concentration increased from 31.0% to 34.7%. For Venturi B, the flow was 20.33 litre min^{-1} at 0 kPa, decreasing to 18.69 litre min^{-1} at 1.8 kPa. The inspired oxygen concentration increased from 35.1% to 36.2%.

As the pressure increased, the strap reading overestimated the actual pressure (table I).

As the volume of the two bags increased, compliance increased progressively and there was virtually no difference in compliance between the new and used bags (fig. 5).

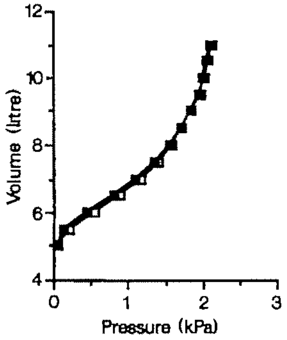

FIG. 5. Compliance of the system. □——□ = New bag; ■——■ = worn bag.

TABLE I. *The characteristics of the Ambu Venturi with increasing pressure in the airway. Two Venturis were assessed after Venturi A was found to have a partially blocked orifice causing the air entrainment to be lower than expected. The strap on the side of the reservoir bag was set intially to zero when the manometer reading was zero. Each value shown is the mean of three readings*

	Manometer reading (kPa)				
	0	0.5	1.0	1.5	1.8
Strap reading	0	0.5	1.2	1.7	off scale
Venturi A					
Flow in circuit (litre min^{-1})	18 69	17.34	13.76	12.26	11.49
Oxygen delivered (%)	31.00	31.75	32.50	32.85	34.70
Venturi B					
Flow in circuit (litre min^{-1})	20.33	19.86	19.42	18.86	18.69
Oxygen in circuit (%)	35.10	35.25	35.50	35.93	36.20

TABLE II. *The pressure decrease (kPa) measured across the Ambu CPAP valve. The valve was adjusted to each setting with a flow of 20 litre min^{-1}, and the flow was then varied between 10 and 70 litre min^{-1} while the actual pressure change was measured with the manometer. Measurements were made as flow was increased to 70 litre min^{-1} (up), and again as flow was decreased to 10 litre min^{-1} (down)*

	Pressure set at 20 litre min^{-1} (kPa)							
	0.5		1.0		1.5		2.0	
Gas flow (litre min^{-1})	Up	Down	Up	Down	Up	Down	Up	Down
10	0.48	0.48	0.99	0.98	1.48	1.48	1.95	1.94
20	0.50	0.50	1.0	0.99	1.53	1.52	2.00	1.99
30	0.54	0.54	1.03	1.01	1.55	1.53	2.01	2.00
40	0.58	0.55	1.07	1.04	1.57	1.55	2.01	2.00
50	0.61	0.57	1.07	1.05	1.60	1.58	2.04	2.03
60	0.61	0.60	1.08	1.05	1.61	1.58	2.08	2.07
70	0.64		1.06		1.59		2.09	

Characteristics of the Ambu CPAP valve

There was a slight increase in pressure as flow across the valve increased. This was least when the valve was set at 1 kPa (table II). There was also a hysteresis between pressures measured whilst flow was increased and decreased, the pressure being slightly lower during the decreasing phase. The pressure was consistently 0.16 and 0.18 kPa greater at all flows when the valve was held outlet-upwards, compared with outlet-downwards (table III).

Pressure variation during the ventilatory cycle

At a constant flow, the pressure in the bag (*PB*) was 0.1 kPa greater than at the Y-piece (*PY*) at all values of CPAP (table IV). When 500-ml tidal volumes were inspired by the simulated lung, *PY* and *PB* fluctuated, decreasing to less than their set values during inspiration and increasing above them during expiration. As CPAP increased between 0.2 kPa and 1.6 kPa, the fluctuation of *PY* declined from 0.4 kPa to 0.16 kPa. The fluctuation in *PB* decreased from 0.16 kPa to 0.07 kPa between 0.2 kPa and 1.6 kPa CPAP. At 1.6 kPa CPAP, the increase in *PB* during expiration disappeared, and the fluctuation resulted only from the decrease in pressure during inspiration (fig. 6).

DISCUSSION

Venturi

Although large compliant bags and adjustable valves have been used to deliver CPAP, they required a supply of 20–30 litre min^{-1} of fresh gas to buffer the effects of the ventilatory cycle. In contrast, this Venturi driven system uses only 3.5 litre min^{-1} of oxygen, but still supplies 20 litre min^{-1} of gas to the patient circuit. One of its major features is that it is more economical than many other devices. Increasing the CPAP decreased the pressure change across the Venturis and this

TABLE III. *Variation in pressure decrease measured across the Ambu CPAP valve with the valve in the horizontal, distal end upwards and distal end downwards positions. The valve was set to 1.0 kPa with a flow 20 litre min^{-1} whilst in the horizontal position. Measurements of actual pressure change were made using the manometer at flows between 10 and 70 litre min^{-1}*

Gas flow (litre min^{-1})	Pressure decrease across CPAP valve (kPa)			
	Upwards	Horizontal	Downwards	Max. diff.
20	1.11	1.00	0.94	0.17
30	1.13	1.00	0.95	0.18
40	1.14	1.03	0.96	0.18
50	1.16	1.04	0.98	0.18
60	1.15	1.07	0.98	0.17
70	1.16	1.09	1.00	0.16

TABLE IV. *Fluctuation of pressure in the bag (PB) and at the patient Y-piece (PY) recorded throughout the ventilatory cycle as CPAP was increased from 0.2 kPa to 1.6 kPa. PY includes the initial transient "opening" pressure of the valve*

	CPAP (kPa)			
	0.2	0.6	1.2	1.6
PY (kPa)	0.40	0.23	0.30	0.16
PB (kPa)	0.16	0.10	0.08	0.07

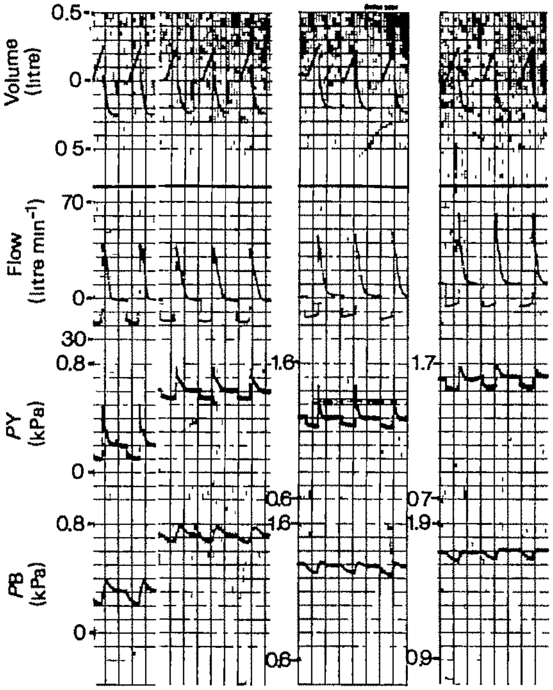

FIG. 6. Traces obtained during simulated spontaneous breathing at 0.2, 0.6, 1.2 and 1.6 kPa CPAP. The pressure was set at the Y-piece. The zero was offset on the *PY* and *PB* traces to record pressures at 1.2 kPa and again at 1.6 kPa. Inspiratory flow is negative on the trace.

reduced air entrainment and total gas flow in the circuit. Thus the oxygen : air ratio increased with increasing CPAP. Venturi B exceeded the manufacturer's claim of 33% oxygen in the circuit at all values of CPAP. The flows obtained from Venturi A were much less than expected because of a partial blockage of the Venturi orifice, causing a low oxygen flow and reduced air entrainment. We presume that this was caused by dirt from the hospital pipeline, but it is possible that it was a manufacturing fault. In clinical use, reduced flows would remain unnoticed. Although the entrained air passes through a sintered brass filter, there is no filter before the Venturi jet to prevent silting. As the instructions state, the Venturi cannot be disassembled for cleaning. In addition, the Venturis were rather noisy.

Reservoir bag

The Ambu CPAP bag is constructed from latex and its compliance increases with increasing CPAP. Whilst the bags appear to withstand the pressures at which they would be used clinically without changing their compliance characteristics, extrapolation of the compliance curve (fig. 5) indicates that at approximately 2.3 kPa progressive distension and bursting of the bag would occur without any further increase in pressure. This makes it impossible to generate dangerously high pressures in the patient's airway if the outlet from the circuit becomes obstructed.

CPAP valve

The Ambu CPAP valve acted as a reasonably good threshold resistor, because the resistance decreased as the flow across the valve increased. The Ambu valve performed better than some other designs [12,13] as the pressure decrease across the valve increased only a little as the flow increased. However, the pressure was greater when it was held with its distal end upwards than downwards. This is because gravity acts with the spring in the former position, but against the spring when it is held end downwards. To overcome this, there is a plastic loop on top of the bag-mount to hold the valve in the horizontal position. The pressure change across the valve at each level of flow was higher when increasing the flow in incremental steps than when decreasing it. This hysteresis is characteristic of stress deformation [14], but is seen more often with synthetic materials than with metals.

Airway pressure variation during the ventilatory cycle

In any system where there is airflow resistance in the breathing circuit, the airway pressure decreases during inspiration and increases during expiration. However, if there is a continuous flow in the circuit greater than the patient's inspiratory flow, the resistance sensed by the patient during inspiration is negligible [15] and the characteristics of the CPAP valve govern the pressure change. If the valve acts as a pure threshold resistor, airway pressure during inspiration should not decrease until inspiratory flow exceeds the continuous flow in the circuit. When this occurs, the pressure in the circuit is maintained by the elastic properties of the bag, and decreases as gas in withdrawn from the bag according to its compliance characteristics. Further, during expiration, airway pressure should not increase above the value of CPAP set by the valve if it has threshold characteristics.

PY and *PB* deviated from their settings even though inspiratory flow did not exceed the continuous flow from the Venturi. The valve is therefore not a true threshold resistor, and the bag is necessary to buffer the change in pressure by supplementing the inspiratory flow. Because of the shape of the compliance curve of the reservoir bag, this effect might be expected to decrease as CPAP increases [11] (fig. 5), and the study confirmed this (table IV, fig. 6). *PY* decreased least during inspiration when the CPAP valve was set at approximately 1 kPa (fig. 6), when the threshold properties of the valve are most efficient (table II).

During expiration, the characteristics of the bag are not relevant because, as soon as the pressure in the circuit exceeds that in the bag, the one-way valve closes and diverts all the gas from the Venturi into the bag, and all the expired gas out through the CPAP valve. Following a high transient, expiratory pressure increases to that expected during peak expiratory flow (table II). The initial high transient appears to be a result of inertia in the valve. Expiratory work is related to the area under the expiratory pressure curve. The additional work required to overcome this opening pressure is therefore the area enclosed by this transient peak, and is probably not significant clinically compared with the total work of expiration.

The pressure measured in the bag was consistently 0.1 kPa greater than that measured at the Y-piece, because of the resistance of the one-way valve at the connection of the circuit to the bag mount and that of the circuit (approximately 0.3 kPa $\text{litre}^{-1}\ \text{s}^{-1}$). Although the system was assessed without a humidifier, this would affect the pressure fluctuations during quiet breathing by adding further resistance to the circuit.

In conclusion, this system is well designed and performs adequately. Its economical consumption of fresh gas makes it suitable particularly for long-term use in the intensive therapy unit.

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Br. J. Anaesth. (1989), **62**, 348–349

CORRESPONDENCE

THE BLOOD LANCET IN REGIONAL ANAESTHESIA

Sir,—The success of regional anaesthesia depends upon accurate placement of local anaesthetic solution in the proximity of nerve trunks [1] without causing sequelae such as neural lesions and damage to blood vessels, tendons, muscles or pleura [2–6]. The classic methods of locating nerves used the production of paraesthesiae with the standard bevel needle. New techniques have been developed which use neurostimulation [7, 8] and atraumatic bevelled needles [9] of the "short bevel" and "pencil point" type.

Neurostimulation as a method of locating the neural plexus requires the use of needles insulated along their entire length except for the point [10, 11]. This offers a more favourable geometry to the zone of depolarization [12]. The use of the short bevel or pencil point needle was promoted by Whitacre in 1951 [13] and more recently by Selander [14] and Galindo [9, 15]; a number of retrospective studies have directly related the incidence of nerve lesions to the technique used and the bevel of the needle [3, 4].

However, there may be difficulty in introducing a relatively blunt needle through the skin of the patient, and the insulation may act as a brake, thereby impeding smooth passage. We have been able to overcome this problem by making a small incision with a surgical blade after a subcutaneous infiltration with local anaesthetic. Alternatively, the blood lancet may be used. Because of its configuration it breaks only the epidermis and the dermis and creates the appropriate orifice for the atraumatic introduction of 20–25 gauge needles.

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EFFECT OF SUXAMETHONIUM GIVEN DURING RECOVERY FROM ATRACURIUM

Sir,—Whilst I agree with almost all the comments in the paper by Dr Scott and Professor Norman [1], my own observations using the Datex Relaxograph in similar situations incline me to be less conservative in my advocacy of *small* doses of suxamethonium to produce brief abdominal relaxation during recovery from non-depolarizing block with atracurium and vecuronium. We have shown [2] that small doses (25–50 mg) can reduce the fluctuations in airway pressure produced by a recovering diaphragm whilst at the same time causing an increased evoked response in the hand.

The authors cite previous findings that the effect on hand muscles of a given dose of suxamethonium depends on the degree of recovery from the underlying non-depolarizing block. Early on, when the residual block is still considerable, there may be no observable depolarizing effect, or it may be limited to a partial transient antagonism of the block; later, the depolarizing effect may produce a biphasic response, antagonizing the non-depolarizing block initially before superimposing a depolarizing block (it is even possible to record a tri-phasic response, as the depolarizing effect antagonizes the non-depolarizing block during both offset and onset). When the non-depolarizing block has recovered to the point where both T1 and T4 have reached 100%, the depolarizing effect can be expressed only as a transient reduction in both evoked responses, with a T4 fade still prominent on recovery; when administration of the dose of suxamethonium is delayed further, the reduction in evoked responses becomes more profound, and the T4 fade on recovery is much less prominent, presumably reflecting the decay of that part of the non-depolarizing effect which is present, but unrecordable. As recovery of the diaphragm from non-depolarizing block is more rapid than that of the hand [3], it is understandable that a small dose of suxamethonium may partially antagonize a degree of non-depolarizing block in the hand, whilst simultaneously producing overt relaxation in the diaphragm, where the recovery from the block is much further advanced.

The use of small doses of suxamethonium affects policy on the use of neostigmine. A maximum of 75 mg of suxamethonium, given in increments of 25 mg, has always provided abdominal relaxation of sufficient duration for my surgeons to complete peritoneal closure. Usually it takes at least a further 10 min before the dressings are applied, by which time, T1 and T4 have always completed their rapid recovery from the depolarizing effect, and have returned to a time-course consistent with continuing recovery from non-depolarizing block. If I give even a small dose of neostigmine at this stage, there is always accelerated recovery, although a further small dose may be required to complete it. There is never accentuation of the depolarizing block, because it is even more transient than in the observations of Dr Scott and Professor Norman for 3 mg kg^{-1} of suxamethomium.

I am prepared to avoid the use of neostigmine (e.g. after a colonic anastomosis and conservative dosing with atracurium), as the abdominal tightness probably implies that adequate ventilatory power will soon return, but I would be less optimistic regarding spontaneous recovery from non-depolarizing block with the use of longer-acting agents. Having used the Datex Relaxograph innumerable times to convince myself of the safety of this approach within these constraints, I am now prepared to use this approach without neuromuscular monitoring.

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Sir,—We agree entirely with Dr Black's claim that small doses of suxamethonium may produce diaphragmatic relaxation during recovery from a non-depolarizing drug but antagonize the more slowly recovering block in the hand. It is well known that the margin of safety for neuromuscular transmission differs between the diaphragm and the adductor pollicis muscle [1]. However, the intercostal and upper airway muscles are probably more sensitive than the diaphragm [2, 3], and this sensitivity may be closer to that of adductor pollicis.

A variety of electromyographic and mechanomyographic approaches to monitoring diaphragmatic and abdominal wall muscle relaxation have been described, none of which seem to be entirely satisfactory and certainly not for routine use. Nevertheless, we recommend that, if anaesthetists are to administer suxamethonium during a recovering non-depolarizing block, they should follow Dr Black's example. A peripheral nerve stimulator will be useful, especially while gaining experience with this technique.

R. P. F. Scott
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BOOK REVIEWS

Automation in Anesthesia—A Relief? By A. P. Meijler. Published (1987, canvas softback) by Springer-Verlag. Pp. 181; illustrated. Price DM 89.

This book carries the subtitle "A Systematic Approach to Computers in Patient Monitoring", which is perhaps a more accurate reflection of its content than the first title. It is described in the preface by the author as "a revised version of my Ph.D. thesis". It is a publication which I enjoyed reading immensely because of my own research interests, but it may have only a limited appeal to the generalist.

Following a brief introduction on the history of monitoring and necessary equipment, the author analyses the role of the anaesthetist (using useful flowcharts), the data he must acquire, the way they are displayed, and the methods of evaluating those which are relevant. It continues to consider man–machine interactions, the automated display of physiological data and critical incident analysis. All these topics are presented primarily in relation to cardiac surgery. Because the book is designed for a multi-disciplinary audience, there are a few descriptions of the basic tasks of an anaesthetist which readers of this Journal would wish to omit.

Much of the book concentrates on describing the Data Acquisition and Display System (DADS) developed by the author and co-workers. The philosophy behind this and the decision making processes related to what to monitor and how to develop the criteria of what a significant change actually is, are extremely thought-provoking for anyone involved in anaesthesia and critical care. Data storage and presentation are given an equally rigorous treatment and the effect of DADS on patient management is tested in clinical systems. The chapter on ergonomics is one of the clearest accounts I have seen written on the problems and possible solutions surrounding the man–machine interface. The standard of the text is maintained in short sections on automated record keeping and critical incident analysis. The referencing is clear and up to date, there are few typographical errors and the illustrations are of a high standard.

In summary, this is a valuable book for those interested in its subject matter. However, despite the fact that it is both short and not excessively expensive, it is not a text for the general anaesthetist or for those preparing for examinations. Realistically, it is more likely to be purchased by libraries than by individuals.

P. Hutton

A Manual of Anaesthesia for Emergency Surgery, 1st Edn. Edited by J. H. Donegan. Published (1987) by Churchill Livingstone, London. Pp. 403; illustrated; indexed. Price £22.50.

There are few books dealing specifically with anaesthesia for emergency surgery. Harry Thornton edited a hardcased book *Emergency Anaesthesia* as long ago as 1965 and this went into a second edition in 1974; more recently, two softcased, pocket sized books have appeared: first, from the United Kingdom, *Handbook of Emergency Anaesthesia* written by Anne Sutcliffe in 1983 and second, a joint Anglo–American book, *Emergency Anaesthesia* edited by Tony Adams, Penny Hewitt and Mark Rogers in 1986.

Judith Donegan from San Francisco has now collected 23 contributors to write on all the usual aspects of anaesthesia for emergency surgery. Although there are no contributors from outside the U.S.A., the overall approach to the many and varied problems differs little from anaesthetic practice in the United Kingdom. However, this reviewer does not accept that a small dose of a non-depolarizing drug before the administration of suxamethonium has any place in the emergency situation.

The plan of the book is to consider all the usual special situations, such as vascular surgery, paediatrics, obstetrics, in a comprehensive manner and thus in much the same format as *Emergency Anaesthesia*. There are also useful additional chapters on dealing with patients suffering from poorly controlled hypertension, diabetic ketoacidosis, shock, sepsis and alcohol abuse, which do not appear as specific chapters in the other books, but there are no separate chapters on monitoring, complications, the liver, or how to deal with mass casualties.

References and suggested reading lists appear after each chapter and some of these are usefully allocated to sub-sections. The trade names of drugs often appear in place of generic names. Features of Sutcliffe's book which do not appear in the other two books are the chapters on anaesthesia in relation to specific conditions, most of which are uncommon, and a useful list of drugs which may interact with anaesthetic agents.

A Manual of Anesthesia for Emergency Surgery is very much a manual, but is unfortunately too large to fit in the pocket of a white coat. The reader may find that the endless lists with numerous numbered and lettered sub-sections and further sub-sections makes reading rather difficult; some chapters offend more than others in this respect. However, it is packed with information and is a valuable addition to the anaesthetist's bookshelf.

A. P. Adams

A Bibliography of References to Anaesthesia in the Australian Medical Journals 1846–1952. By Gwen Wilson. Published by The Faculty of Anaesthetists Royal Australasian College of Surgeons. Pp. 481; indexed.

This book is organized in a number of sections covering aspects of anaesthesia and anaesthetic related techniques. In all there are 17 sections, most of which have sub-sections.

Sections 1, 2 and 3 are probably those of most interest as these cover agents, apparatus and techniques. The section on agents includes a valuable sub-section on the many miscellaneous volatile agents used during the search for perfect anaesthetic agents, in addition to premedication, sedatives and opioids, local anaesthetic agents and drugs used in relation to anaesthesia. The section on apparatus includes sub-sections on regional anaesthetic apparatus, blood transfusion pumps and other related anaesthetic equipment, in addition to standard apparatus. The section on techniques is valuable as it follows the development of anaesthesia, including local anaesthesia. The other sections include specialized techniques, choice of anaesthesia, preoperative, intraoperative and postoperative care, resuscitation, complications and death from anaesthesia.

The section on deaths from anaesthesia provides great background interest, dealing with not only death associated with chloroform, but also death associated with other anaesthetics. Further sections include anaesthetic records and monitoring, basic sciences, history, education, obituaries, books, remuneration and status, and are of background interest to the anaesthetic historian.

By the nature of its title this book is clearly a reference work which will be invaluable for those researching the development of anaesthesia, primarily in Australasia. However, because of the nature of anaesthetic practice, what was reported in these journals is, in fact, a record of development of anaesthesia. The subjects are well covered and the presentation of the references adequate, although the occasional misprint slips in. One area of most value throughout all the sections comprises those references related to the period of the mid 1940s to 1962. This provides an insight into the development of anaesthetic practice today and reminds one of the passing of those agents which have not stood the test of time.

This book is going to be an essential volume for the anaesthetic historian as it provides such a valuable reference sequence for the development of anaesthesia during the period from 1846 to 1962. Although a pure reference volume, the print size makes it easy to read.

I. McLellan

Pulmonary Function Indices in Critical Care Patients, 1st Edn. By J. X. Brunner and G. Wolff. Published by Springer-Verlag, Berlin. Pp. 171; indexed; illustrated. Price 98 DM.

This short book is an extended Ph.D. Thesis, and there seem to be several reasons for it to be published in its present form. It describes the development of a method for measuring some aspects of lung function in clinical circumstances. The authors suggest that, if these tests were applied more widely, the changes in function that occur in patients during intensive care would be understood better and their management would become more rational. The argument is logical, but one suspects that only academics would be willing to undertake such a project. When given a "simple" device such as a pulse oximeter or a straightforward method for cardiac output measurement, where the relationship between changes in treatment and the resultant changes in measurement is obvious, most clinicians would incorporate such devices into their clinical practice. However, the complete system described here provides an array of measurements that many might find difficult to comprehend simultaneously. Functional residual capacity, lung compliance and airway resistance are fairly simple concepts, but what of the measurable part of the series deadspace, the washout efficiency, and the accessible pulmonary volume? This book explains these concepts and, in doing so, covers large tracts of pulmonary physiology, but the explanations are necessarily terse. Unless the reader has already encountered the concepts involved, and is familiar with the literature, the authors' explanations are difficult to comprehend. For example, the operating principle of the quadrupole mass spectrometer is described in 20 lines of text, and the six inert gas technique summarized in a mere 11. Consequently, the authors urge their readers to look further, to sources such as the American Physiological Society handbook. In addition, there is the occasional subtle problem with translation that could confuse the unwary, such as the "linearity of the statistic pressure measurement", the use of "apparently" instead of "it is apparent...", "imminent" weakness instead of "intrinsic", and the statement that ventilation and perfusion do not ideally match up, which is not the same as saying they do not match up ideally. In addition, the use of symbols is not consistent with convention: CO is used instead of Qt, V′ instead of $\dot{V}$, $\mathrm{F}_{\mathrm{CO_2,et}}$ instead of $F\mathrm{E}'_{\mathrm{CO_2}}$. Such examples suggest that the author of the foreword was optimistic in expressing the hope that respiratory physiology in the book can be presented in the "language of the clinician". It seems that respiratory physiology only developed rapidly as a subject because a system of terms and concepts was developed specifically for use in the field, allowing analysis and quantification; to attempt to re-translate the jargon into simple clinical parlance is difficult.

However, the major purpose of the book is given in the preface: to save researchers the "first five unpleasant years" of setting up a complex system for measuring lung gas exchange, and mechanics. To do this, the authors have presented their painstaking approach to measurements of mechanics, washin, FRC, and gas uptake and production, together with accounts of the relevant physiology and technology. I found the book worth reading for this alone, particularly the beautiful hydraulic lung model.

Once the authors had set up their system, which was essentially a mass spectrometer, pneumotachograph and oesophageal balloon, they tested it in paralysed sedated patients undergoing ventilation after cardiac surgery, and obtained some interesting results; however, the clinical relevance is justified on the basis of essentially anecdotal studies. This reviewer would have welcomed more convincing evidence that the "first five painful years" were worth it, in terms of consistently improved patient management, and that the indices derived and measured are truly clinically valuable, by influencing outcome.

G. B. Drummond

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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL I

PREDICTING THE SPREAD OF SPINAL ANAESTHESIA

There are few techniques which produce so widespread an effect in response to the administration of so little drug as the subarachnoid administration of a local anaesthetic agent. Total block of all the modalities of nerve function may be produced in up to two-thirds of the body with minimal risk of systemic drug toxicity. Of course, there are potential problems: the risk of neurological sequelae, headache produced by leakage of CSF, hypotension and inadequate block are matters that concern all anaesthetists who use the technique. As a result of the attention that has been drawn to the first three of these complications, strategies exist for their prevention or treatment.

The production of an adequate subarachnoid (spinal) block has two components. First, it is essential to ensure that the local anaesthetic is injected into the cerebrospinal fluid (CSF). Fine gauge needles are essential to prevent headache, but they are displaced easily during the injection. Thus great care must be taken to avoid depositing the solution in the extradural space. Second, in order to predict the height of block attained, an understanding is required of the factors that govern the spread of local anaesthetic solutions through the CSF. A great deal of research in the past 10 years has been devoted to this objective and the results have been reviewed and summarized [1, 2] to provide a guide to the selection of an appropriate technique [3].

The "easy" classical option is to inject a hyperbaric solution, place the patient supine and allow the solution to spread to the mid-thoracic level. This approach carries the inherent defect that an extensive sympathetic block results in an increased risk of cardiorespiratory complications.

Unfortunately, the use of a technique which might result in less extensive spread of anaesthesia carries the risk of inadequate block in some patients. Most studies of spinal anaesthesia have concentrated on examining the effects of changes in anaesthetic procedure on the mean spread of analgesia in a group of patients. Although some attention has been drawn to the range of spread of analgesia, few workers have examined the factors responsible for the variability in extent of block in different patients. The accompanying study by Tuominen, Taivainen and Rosenberg [4] examined the injection of plain 0.5% bupivacaine at either the second or the fourth lumbar interspace in supine subjects. The lower level of injection not only resulted in a more restricted mean spread, but also produced a narrower *range* of blocks. A similar study [5] (which also found a difference in mean spread) did not demonstrate any differences in the range of blocks. However, there were some differences of detail in the two studies, most notably that the earlier investigation compared injection at the second with the third lumbar interspace, rather than the fourth.

Both studies found that the lowest level of block was the same (L2) following injection at any of the three lumbar levels. The present study suggests that injection at the fourth interspace results in much less risk of extensive thoracic block. Only two of 20 injections resulted in spread of analgesia above T8, whereas similar extension of analgesia occurred in 10 of the 20 patients who received spinal injection at the higher level. It was not possible to produce confidently, with injection at any level, a block higher than that required for knee surgery, but the risk of hypotension was decreased by injection at the lowest level; in essence this produced a block that was more predictable.

It is interesting to speculate on the mechanism of this effect. The lower the level of injection, the more likely is the solution to be deposited in the lumbar CSF collection and it may be that this "buffers" the initial spread of solution because of bulk displacement. Injection at a higher level might cause greater spread along the narrow space between dura and spinal cord or cauda equina.

There is some support for this hypothesis from two sources. A study of the effect of removing CSF before injection [6] showed that spread was both more extensive and more variable after initial removal of CSF, implying that the buffering ability of the lumbar collection had been impaired. Similarly, increasing the volume injected has been shown to have more effect on the range of blocks than on mean spread [7].

It is important to emphasize that the experimental data and deductions presented here are confined to spinal anaesthesia practised in precisely the method described in these studies. Alteration in the technique, for example lumbar puncture in a sitting rather than a horizontal patient, may produce different results, especially with plain bupivacaine, which is a hypobaric solution. In future, the design of any research on spinal anaesthesia should permit examination of factors which affect inter-patient variability in block.

J. A. W. Wildsmith

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EDITORIAL II

PULSE OXIMETERS: ESSENTIAL MONITORS WITH LIMITATIONS

Maintaining an adequate supply of oxygen to vital tissues is a fundamental responsibility of all medical practitioners and is one that weighs especially heavily upon anaesthetists. Failure to do so may result in death or, "a fate worse than death", severe brain damage [1]. Given that detection of hypoxaemia by clinical signs alone is notoriously unreliable [2], it is hardly surprising that pulse oximetry has been adopted rapidly and enthusiastically by anaesthetists, especially in the U.S.A. and increasingly in the U.K. Indeed, a pulse oximeter has become a prominent component of minimal monitoring recommendations [3]. Critical appraisal of this new technology requires knowledge of how it functions and hence its limitations.

Pulse oximeters operate on the principle of absorption spectrophotometry and rely on application of the Beer and Lambert Laws [4]. Haemoglobin and oxyhaemoglobin absorb light of different wavelengths to different extents. A pulse oximeter probe constructed of two photodiodes, one producing red and the other infra-red light, and a single photodetector is placed over a convenient vascular bed. The photodiodes are controlled by a microprocessor and are switched on and off in sequence many times per second. The photodetector output is resolved into a plethysmographic waveform for each colour of light. Only the pulsatile components of these waveforms, some 1–5% of each signal, are processed. The changes in the amount of red and infra-red light absorbed and hence the amount of light reaching the photodetector, are assumed to result from the effect of a volume of arterial blood containing haemoglobin and oxyhaemoglobin entering the vascular bed. The ratio of the pulsatile components is computed and the corresponding oxygen saturation "looked up". Typically, these pulse saturation figures are averaged over 2–16 s, the actual averaging period normally being user selectable. Pulse rate is calculated from the reciprocal of time between successive pulses.

In the above process there are a number of deviations from the strict conditions under which the Beer and Lambert Laws hold true and therefore arterial oxygen saturation (Sa_{O_2}) cannot be deduced by theory alone. Individual manufacturers have developed algorithms which include experimentally derived correction factors for these deviations and for the variable light emitting characteristics of some diodes. Each manufacturer relies on empirical calibration and, typically, quotes accuracy as ±2% in the 70–100% range of Sa_{O_2} values.

As current pulse oximeters use only two wavelengths of light, the presence of only two chromophores can be measured, in this case haemoglobin and oxyhaemoglobin. The presence of other light absorbing moieties such as carboxyhaemoglobin, methaemoglobin, bile salts or exogenous dyes, notably methylene blue, leads to inaccuracies in estimation of Sa_{O_2} [4–8]. Any patient with unexplained cyanosis, suspected of having a dyshaemoglobinaemia or a history of smoke inhalation, should have a blood sample drawn for laboratory analysis by co-oximetry. Co-oximeters measure the absorption of four or more wavelengths of light and can therefore measure the presence of four chromophores: haemoglobin, oxyhaemoglobin, carboxyhaemoglobin and methaemoglobin.

Because of the need for empirical calibration in any particular model, there is often little information on the accuracy of any model below 70% Sa_{O_2}. A few datum points may be collected serendipitously from those patients in whom severe desaturation occurs and persists despite therapeutic intervention [9, 10]. However, these are scarcely sufficient for an organized testing programme. Severinghaus and Naifeh have attempted to overcome this problem by a complicated procedure allowing the induction of transient profound desaturations in healthy volunteers [11]. Great variations in pulse oximeter performance were seen and at least one manufacturer altered its algorithm on the basis of these results. Work with prototypes for two major manufacturers has confirmed the importance of fine tuning the algorithm, particularly at low saturations (Kidd J.F. and Johnston K.R. – unpublished observations).

Hypotension with vasoconstriction reduces the pulsatile component, and ambient light impinging on the photodetector increases the total signal [12, 13]. Both cause the pulsatile component of the plethysmographic waveform to decrease to less than its normal value of 1–5% of the total signal. Furthermore, motion artefact introduces "noise" and distorts the plethysmographic waveform. These confounding factors make it more difficult to distinguish what is, or is not, a true pulse and may lead to machine failure, a prolonged machine response time or inaccurate estimation of Sa_{O_2}. Manufacturers programme a variety of strategems into their respective algorithms to combat this difficulty, the precise details of which are regarded as commercial secrets. However, no matter how sophisticated the subsequent software manipulation, pulse oximeter performance depends ultimately on the quality of the raw signal. This signal is best presented as a plethysmographic waveform without automatic gain, thereby allowing the operator to make his or her own assessment of any perfusion or motion artefact problem and of the likely veracity of the displayed value of Sa_{O_2}. Good probe design should prevent ambient light interference and ensure a stable subject–probe interface. Yelderman and Corenmen [14] have suggested the use of a special nasal probe to ameliorate the problems of vasoconstriction and hypotension, claiming that pulsation of the anterior ethmoid arterial supply to the nasal septum persists over a wider range of pressures that the finger pulse. Furthermore, unlike measurements at a finger which are subject to a time lag caused by the vasoconstriction, measurement via the nasal septum should quickly reflect any changes in saturation of blood supplying vital structures. Machine response time can be minimized by the operator selecting the shortest convenient saturation averaging time, thus producing the quickest overall indication of central changes in saturation.

In view of the above, it has been suggested [15] that areas for further research to develop an improved second generation of pulse oximeters should include:

(1) Better understanding of the sources of motion artefact so that optimal corrective measures can be taken;

(2) development of reflectance pulse oximetry so that measurements may be made anywhere on the body surface;

(3) use of additional wavelengths to reduce errors produced by the presence of other haemoglobin species;

(4) methods of determining the accuracy of pulse oximeters before their use on patients [15].

Of these, measurement at additional wavelengths would involve considerable practical and computational difficulties and extra expense which would probably outweigh the small number of cases in which it would be of major importance. The most pressing need is to develop appropriate models to allow objective comparative testing of the accuracy, low-flow performance, motion artefact rejection and response time of the numerous pulse oximeters on sale in the U.K.

The present issue of the Journal contains a study directed towards some aspects of this problem [16]. Guidance may emerge when the Ministry of Health publishes a Health Equipment Information (H.E.I.) issue on pulse oximeters. Despite adequate advance warning, this will probably be too late to influence a major proportion of the large sums (£1500–4000) now being spent on instruments with which anaesthetizing locations, recovery rooms and high dependency nursing areas are now being equipped.

Nevertheless, the present generation of pulse oximeters are normally extremely easy to use, require no calibration by the user and are clearly superior to clinical signs in the recognition of hypoxaemia, no matter how experienced the clinician [17, 18]. As yet, there is no evidence of a reduction in anaesthetic-related morbidity and mortality attributable to the deployment of pulse oximeters. However, such a benefit may reasonably be expected. If death or injury subsequent to an anaesthetic mishap is to be avoided, the time taken to detect an abnormality, ascertain the cause(s) and effect a remedy must be less than that required to induce tissue damage. Every effort must be made to increase the time available for effective remedial action. Use of pulse oximetry can lead to faster detection of hypoxaemic incidents during anaesthesia and, therefore, to swifter institution of an effective remedy.

Pulse oximeters are not inexpensive, but neither are medico–legal settlements for brain damage. Some malpractice insurers in the U.S.A. now offer a discount on premiums to those anaesthetists who undertake to use a pulse oximeter routinely (and a capnograph when a tracheal tube is *in situ*). They are thus in no doubt that there will be a reduction in anaesthesia-related morbidity and mortality as a consequence of the routine use of pulse oximeters. It seems not unreasonable to expect an improvement in the U.K. also, although it may well transpire that the major benefits will come from improved monitoring during induction and recovery than during maintenance of anaesthesia.

J.F. Kidd and M.D. Vickers

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Br. J. Anaesth. (1989), **62**, 358–361

SPREAD OF SPINAL ANAESTHESIA WITH PLAIN 0.5% BUPIVACAINE: INFLUENCE OF THE VERTEBRAL INTERSPACE USED FOR INJECTION

M. TUOMINEN, T. TAIVAINEN AND P. H. ROSENBERG

SUMMARY

Three millilitre of plain 0.5% bupivacaine was injected intrathecally at two different levels in two groups of 20 patients. Injection at the L2/3 space produced a significantly higher spread of analgesia (mean T7 (SD 3.9)) than injection at L4/5 (T11(1.8)). The range of the cephalad spread of the block was less in the L4/5 group ($P < 0.001$ at 60 min). The spread of anaesthesia continued beyond 30 min in both groups. In all patients anaesthesia sufficient for surgery of the knee and the foot was achieved. One patient had a final block level of T1 after injection at L2/3, accompanied by transient arterial hypotension.

Prediction of the final level of a spinal block is poor when plain bupivacaine is used as the local anaesthetic [1–4]. Wide variation in the spread of the block has been observed, even when the same space has been used for the injection of the same volume of local anaesthetic [5, 6]. However, spread to a predictable segmental level which avoids haemodynamic complications would be a useful characteristic.

A volume of 2.7 ml of plain 0.75% bupivacaine resulted in a clinically greater extent of analgesia, accompanied at times by arterial hypotension, when injected at L2/3 instead of L3/4 [7]. In controlled studies, a volume of 3 ml of plain 0.5% bupivacaine injected at L3/4 for spinal anaesthesia provided satisfactory conditions for surgery of the lower limb [1,3,6,8–10).

This study was undertaken to determine if injection of the same volume (3 ml) of plain 0.5% bupivacaine at a higher or lower spinal interspace could improve prediction of the level of the subsequent spinal block.

PATIENTS AND METHODS

Following Ethics Committee approval, we studied 40 patients, aged 22–59 yr (ASA I), scheduled to undergo orthopaedic surgery of the lower extremity. The patient data, type of surgery and its duration are shown in table I. Patients aged less than 20 yr or more than 60 yr and those outside the normal range of body mass index (BMI) values for Finnish adults [11] were excluded from the study. All patients received diazepam 0.15 mg kg^{-1} by mouth for premedication. In the operating room, an infusion of Ringer's solution was started and a volume of 6 ml kg^{-1} was administered during the 30 min following the subarachnoid injection.

Spinal anaesthesia was performed with the patient lying in the lateral horizontal position

TABLE I. *Patient data. Number of patients or means (SEM)*

	Group L2/3	Group L4/5
Sex (M/F)	10/10	11/9
Age (yr)	37.7 (2.5)	35.8 (2.0)
Weight (kg)	66.8 (2.2)	68.1 (2.1)
Height (cm)	169.4 (2.1)	172.4 (2.1)
Body mass index (kg m^{-2})	23.1 (0.3)	22.8 (0.3)
Type of surgery (No.)		
Thigh	2	—
Knee	16	15
Ankle or foot	2	5
Use of tourniquet (No.)	18	19
Tourniquet time (min)	88.4 (7.2)	82.8 (6.6)
Time from injection to end of operation (min)	106.5 (8.4)	108.3 (8.4)

This article is accompanied by Editorial I.

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using a 25- or 26- gauge spinal needle with plain 0.5% bupivacaine 3 ml at room temperature (sp.gr 1.004). In random order, 50% of the patients received the injection at the L2/3 space and the other 50% were injected at L4/5. The determination of the interspace for the puncture was always made by two anaesthetists. The spines of the vertebrae were counted from both cranial and caudal directions and palpation of the iliac crest was made to confirm the position of the fourth lumbar vertebra. All punctures were made in the mid-line and aspiration of spinal fluid 0.2 ml was made at the beginning and at the end of the injection of bupivacaine which was made over 15 s. Thereafter, the patients were moved to the supine horizontal position. Pinprick analgesia (27-gauge needle) and motor block (Bromage Scale 0–3 [12]) were tested at 5, 15, 30 and 60 min and then at 30-min intervals until the recovery of the L1 spinal segment. The moment when the patient was able to produce a visible contraction in the rectus femoris muscle was taken as the time of recovery from the motor block.

The data were analysed using Student's *t* test for comparison between groups and analysis of variance (ANOVA) within groups. For comparison of the standard deviations Bartlett's χ^2-test, d.f. = 1, was used.

RESULTS

Injection at L2/3 produced a significantly higher level of analgesia than injection at L4/5 ($P < 0.001$ at each testing time) (fig. 1). The interindividual variability of the cephalad spread of analgesia was greater in group L2/3 and there was a significant difference in the standard deviations of the segmental levels between the groups from 5 min to 60 min ($P < 0.001$ at 60 min).

The maximum block (mean (SD)), T7 (3.9) in group L2/3 and T11 (1.8) in group L4/5 (figs 1, 2) was reached within 60 min. The change in spread of analgesia from 15 to 30 min was statistically significant ($P < 0.05$) in both groups. Three patients in group L2/3 and 10 patients in group L4/5 had an increase in the cephalad spread at 30–60 min. All the blocks were symmetrical: no patient developed a block that varied by more than one segment between the two sides of the body.

In all patients, anaesthesia satisfactory for surgery of the foot, knee or thigh (two patients) was achieved. Four patients in group L2/3 and seven in group 4/5 received diazepam 2.5–15 mg, midazolam 2.5–7.5 mg or fentanyl 0.05–0.3 mg

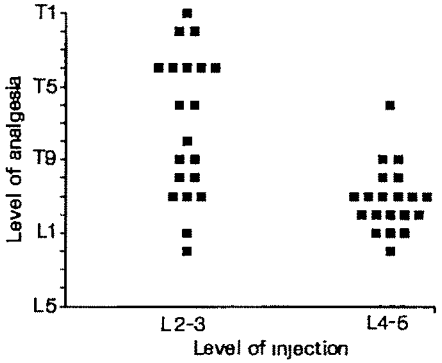

FIG 2. Maximum level of spinal analgesia of 40 patients 60 min after the injection of plain 0.5% bupivacaine at two different spinal interspaces.

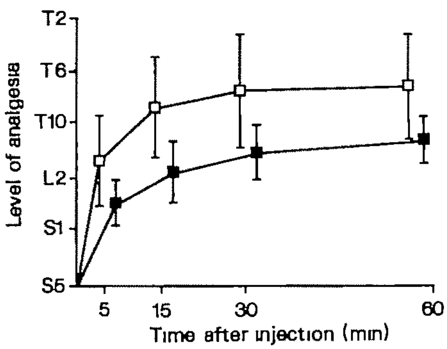

FIG. 1. Mean (SD) onset time of analgesia after intrathecal injection of plain 0.5% bupivacaine 3 ml at level L2/3 (□) and L4/5 (■).

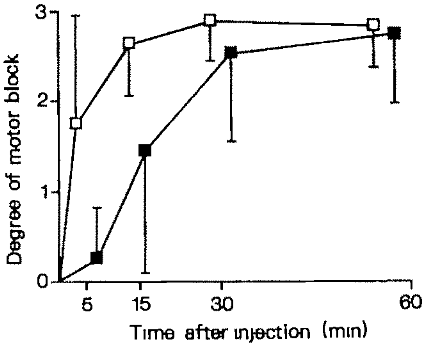

FIG. 3. Mean (SD) onset time of motor blockade of the lower limbs after intrathecal injection of plain 0.5% bupivacaine 3 ml at level L2/3 (□) and L4/5 (■)

for sedation, pain induced by the tourniquet after inflation of the cuff, or both.

In both groups, 18 patients had complete motor block. One patient with injection at L4/5 developed no measurable motor block despite sensory block to T12 (fig. 3).

Mean (SD) time interval from injection of bupivacaine to recovery of the L1 segment was 173 (53) min in group L2/3 and 142 (38) min in group L4/5. Times to the start of motor recovery were 192 (36) min and 169 (39) min, respectively, in the two groups. These differences were not significant.

One patient (female, 30 yr) required ethylphenylephrine hydrochloride 1 mg for a decrease in systolic arterial pressure exceeding 30%. Her final block level was T1 after injection of bupivacaine at L2/3. Another patient (female, 36 yr, 25-gauge spinal needle) developed postspinal headache that was treated successfully with an extradural blood patch on the third day after operation. Her block had reached T12 after injection of bupivacaine at L4/5.

DISCUSSION

There was less variation in the segmental level of sensory block when 3 ml of plain 0.5% bupivacaine was injected at the L4/5 level than after injection at L2/3. In spite of the lower spread of pinprick analgesia, sufficient anaesthesia was obtained for orthopaedic surgery of the knee and the foot with moderate tourniquet inflation times (mean 83 min in the L4/5 group and 88 min in the L2/3 group). In some instances, the slow onset of anaesthesia delayed the clinical preparation of the patient for surgery, but supplementation with fentanyl, diazepam or both made inflation of the thigh tourniquet tolerable before the extremity was fully anaesthetized.

The cause of the wide variation in spread of block when injection was made at L2/3 is unclear. We assume that anatomical properties of the lumbar region may play an important role in the spread of plain bupivacaine in cerebrospinal fluid. This is supported by our recent study which demonstrated an almost identical spread of analgesia when a spinal block with the same dose and at the same space was repeated in the same patient [13]. Higher spread of block is produced by the sitting posture [8], older age [5, 6] and increased BMI [10, 14] of the patient, in addition to warming of the injected solution [9]. These factors were excluded in the present study, and 40% of blocks injected at the L2/3 level reached T4 or even higher.

Although only one patient needed treatment for hypotension in the present study, the injection of local anaesthetic at L2/3 is known to cause hypotension in relatively young adults also [7].

In this study, two anaesthetists identified the spinal interspace and in no case was there disagreement on the location of the injection site. Using radiography, Moore [15] found that, in 50% of subjects, the spinal needle did not rest in the predicted interspace. Therefore, special care should be taken to identify the correct lumbar space in studies evaluating segmental spread of spinal anaesthesia. As shown in the present study, a difference of two lumbar interspaces for subarachnoid injection significantly affects the spread of sensory block.

Spread of analgesia continued for more than 30 min in both groups after injection. If maximal spread of sensory levels is to be compared between study groups, testing should be continued for at least 60 min after injection of plain bupivacaine [6].

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EFFECT OF HIGH THORACIC EXTRADURAL ANAESTHESIA ON VENTILATORY RESPONSE TO HYPERCAPNIA IN NORMAL VOLUNTEERS

T. KOCHI, S. SAKO, T. NISHINO AND T. MIZUGUCHI

SUMMARY

We have investigated, in six healthy male volunteers, the effect of high thoracic extradural anaesthesia on the ventilatory pattern and hypercapnic ventilatory response. Ventilatory variables were determined using a respiratory inductive plethysmograph. Duration of inspiration, rib cage excursion and its contribution to tidal volume decreased significantly following extradural anaesthesia, while mean inspiratory flow rate and minute ventilation increased. End-tidal P_{CO_2} *and the tidal excursion of the abdomen were unchanged. Hypercapnic ventilatory response decreased significantly following extradural anaesthesia, principally because of the rib cage component. The slope of the abdominal component did not change significantly. The results indicate that mechanical impairment of rib cage movement can produce decreased ventilatory response to carbon dioxide. The ventilatory impairment and the changes in breathing pattern induced by the high thoracic extradural anaesthesia probably reflect blockade of the efferent or afferent pathway (or both) of the intercostal nerve roots.*

It is generally accepted that the parasternal intercostal muscles (interchondral part of the internal intercostal muscles) are inspiratory and serve to raise the ribs [1, 2]. Thus reduced power in these muscles could impair outward movement of the upper rib cage and hence reduce ventilation. Furthermore, afferent intercostal nerve activity has been shown to affect ventilatory control [3–5]. Thoracic extradural anaesthesia might affect ventilation by both of these mechanisms. The present study was designed to determine the degree of ventilatory impairment following high thoracic extradural anaesthesia, by measurement of the hypercapnic ventilatory response (HVR).

SUBJECTS AND METHODS

We studied six healthy, male volunteers aged 18–29 yr, who had experienced HVR previously. None had any significant medical history, took regular medication or had recently ingested alcohol. The study was reviewed by our Institutional Ethics Committee and was conducted according to the Declaration of Helsinki. The nature and extent of the investigation had been explained to the subjects and their informed consent obtained.

A 20-gauge cannula was inserted into a forearm vein to permit administration of fluids. Ringer-lactate solution 300–700 ml was administered during the course of the study.

Each subject was placed in the lateral position and an 18-gauge Tuohy needle inserted in the 3rd or 4th thoracic extradural space by the loss of resistance technique. A polyethylene catheter was inserted cranially to a distance of 4 cm into the extradural space. Following removal of the needle, the subject was moved into the supine position and two transducer bands were placed around the trunk, one at the level of the nipples and another at the level of the umbilicus.

Systemic arterial pressure and heart rate were monitored continuously with an automatic sphygmomanometer (Nippon Colin BX-5) and

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an electrocardiograph (Siemens Sirecust 404), respectively.

The respiratory inductive plethysmograph (RIP) (Non-Invasive Monitoring Systems Inc.) was calibrated against spirometry by the least-squares method [6] and checked during tidal breathing in the supine position before and after the study. Data were considered unacceptable if RIP measurements differed from simultaneous spirometry by > 10 %. The volume change of the rib cage (*V*rc), abdomen (*V*ab) and the overall sum (*V*T) derived from the RIP, were recorded on a four-channel recorder (Nihon-Koden RJG4124) together with end-tidal $P\text{CO}_2$ ($P\text{E}'_{\text{CO}_2}$) determined with an expired gas analyser (San-Ei 1H21A).

Duration of inspiration (*T*I), expiration (*T*E) and *V*T were determined from the sum signal of RIP. Breath duration (*T*T), duty ratio (*T*I/*T*T), mean inspiratory flow rate (*V*T/*T*I) and breath-to-breath minute ventilation ($\dot{V}$I) were calculated. $\dot{V}$I was separated into the contributions of the rib cage ($\dot{V}$I,rc) and abdomen ($\dot{V}$I,ab).

The ventilatory response to carbon dioxide was measured by a modified Read rebreathing technique [7]. Subjects rebreathed through a mouthpiece into a 7-litre reservoir charged with 7 % carbon dioxide in oxygen until $P\text{E}'_{\text{CO}_2}$ reached approximately 9 kPa. Expired gas was sampled at 250 ml min^{-1} and returned to the reservoir system.

Variables were recorded continuously during 15 min of quiet breathing and during rebreathing. The subjects were allowed to recover for 30 min following rebreathing and then received 2 % lignocaine 9–12 ml through the extradural catheter. Fifteen minutes later, recording was restarted and the second carbon dioxide rebreathing was performed 25 min after the administration of lignocaine. Dermatome levels of reduced sensation to pinprick were determined before and on completion of rebreathing.

Data analysis

Resting ventilatory variables for pre- and post-extradural anaesthesia were determined from the data measured during the final 1 min of quiet breathing and averaged for each subject. Each fifth breath was analysed during the steady state period of carbon dioxide rebreathing.

Data were analysed using least squares regression for HVR and Wilcoxon's Rank test for comparison of variables between pre- and post-extradural anaesthesia. $P < 0.05$ was regarded as significant.

RESULTS

Anthropomorphic data and extent of extradural block for each subject are shown in table I. The dose of lignocaine varied between subjects, depending on the physical characteristics: subjects 1 and 5 received 2 % lignocaine 9 ml and the others received 12 ml. The mean (SD) number of segments blocked was 6.7 (2.5). Mean arterial pressure during quiet breathing did not change significantly from 77.7 (5.2) mm Hg to 74.3 (7.4) mm Hg, whereas heart rate decreased from 77 (6) to 67 (3) beat min^{-1} ($P < 0.01$). Horner's sign was observed bilaterally in all subjects

Resting breathing patterns

Following thoracic extradural anaesthesia, *T*I decreased significantly, while *T*E remained unchanged (table II). As a result, *T*T decreased significantly ($P < 0.05$). *V*rc decreased significantly ($P < 0.025$), whereas *V*ab was unchanged following extradural anaesthesia (fig. 1). Consequently, the contribution of the rib cage to tidal

TABLE I. *Anthropomorphic data and the extent of extradural block for each subject*

Subject No.	Age (yr)	Height (cm)	Weight (kg)	Upper and lower levels of analgesia	No. of segments	Dose of lignocaine (mg)
1	29	168	54	C5–T7	11	180
2	26	180	82	T1–T5	5	240
3	29	172	60	T2–T5	4	240
4	20	182	70	T2–T7	6	240
5	18	167	61	C7–T6	8	180
6	19	170	59	C8–T5	6	240
Mean	23.5	173.2	64.3		6.7	
SD	5.1	6.3	10.1		2.5	

TABLE II. *Changes of respiratory timing variables and* $P\text{E}'_{CO_2}$ *before and after thoracic extradural anaesthesia (mean (SEM)).* *P < 0.05; **P < 0.025 *compared with control*

	*T*I (s)	*T*E (s)	*T*T (s)	*T*I/*T*T	$P\text{E}'_{CO_2}$ (kPa)
Control	2.05 (0.61)	2.56 (0.57)	4.54 (1.12)	0.403 (0.026)	5.16 (0.20)
Extradural anaesthesia	1.47 (0.23)**	2.10 (0.34)	3.49 (0.50)*	0.420 (0.024)	4.97 (0.28)

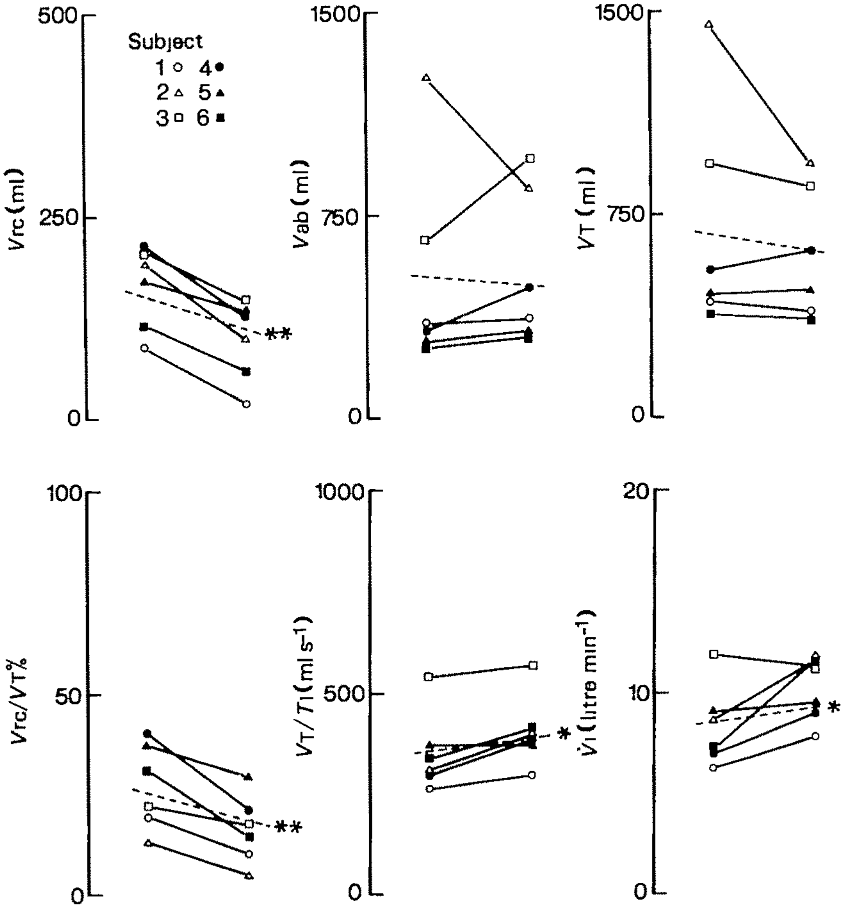

FIG. 1. Changes in tidal excursion of the rib cage (*V*rc), abdomen (*V*ab), overall sum (*V*T), compartmental contribution of the rib cage to tidal volume (*V*rc/*V*T %) mean inspiratory flow rate (*V*T/*T*I) and minute ventilation (*V̇*I), before (left) and following (right) thoracic extradural anaesthesia. ○△□●▲■ = Individual data, — — = mean value. *$P < 0.05$; **$P < 0.025$ compared with control.

breathing (*V*rc/*V*T %) decreased significantly ($P < 0.025$) and, as a result, tidal volume was decreased slightly and not significantly. Mean inspiratory flow rate (*V*T/*T*I) and minute ventilation (*V̇*I) increased significantly ($P < 0.05$), mainly because of the shortened *T*I (fig. 1).

Ventilatory response to carbon dioxide

Figure 2 shows the slopes of the ventilatory response to carbon dioxide for subject 3. The overall response decreased by approximately 25%, because of a reduction in the rib cage

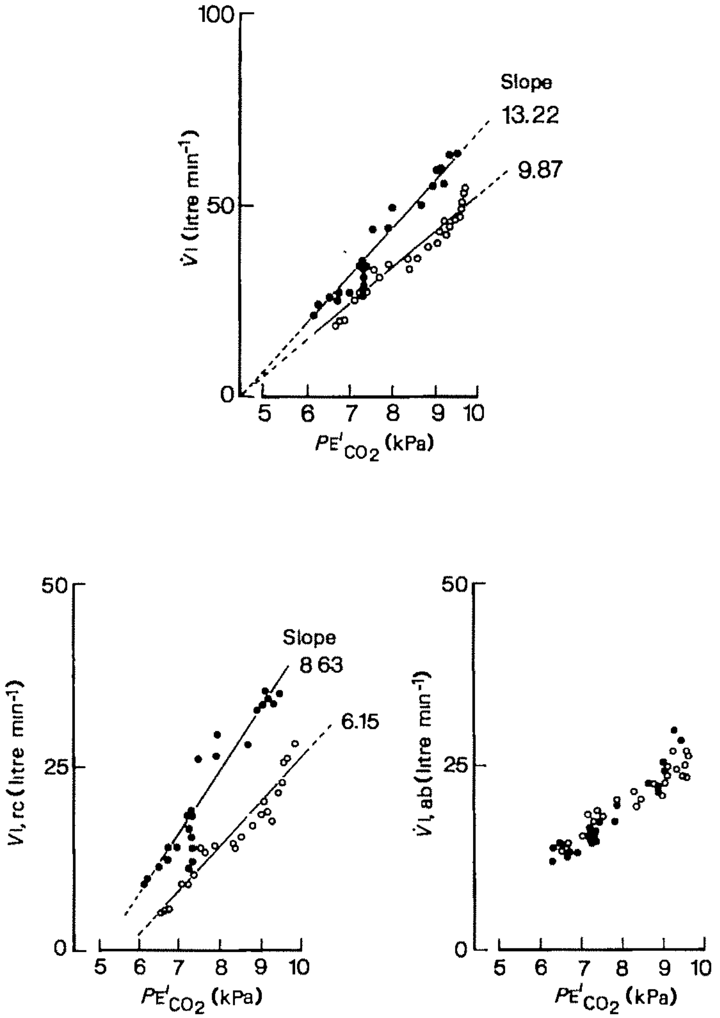

FIG. 2. Ventilatory response to carbon dioxide and its partitioning into rib cage and abdominal components determined in subject 3. ● = Control measurements; ○ = following extradural anaesthesia. Values for Slope are litre min^{-1} kPa^{-1}.

TABLE III. *Slope of the linear relationships of* $\dot{V}_I$, $\dot{V}_{I,rc}$ *and* $\dot{V}_{I,ab}$ *with* $P_{E'CO_2}$ *before and after thoracic extradural anaesthesia. Individual data and mean (SD) of six subjects.* *$P < 0.05$; **$P < 0.025$ *compared with control*

Subject No.	$\dot{V}_I/P_{E'CO_2}$ (litre min^{-1} kPa^{-1})		$\dot{V}_{I,rc}/P_{E'CO_2}$ (litre min^{-1} kPa^{-1})		$\dot{V}_{I,ab}/P_{E'CO_2}$ (litre min^{-1} kPa^{-1})	
	Control	Anaesthesia	Control	Anaesthesia	Control	Anaesthesia
1	14.22	10 05	5 00	1 46	9.23	8.58
2	20 95	18 44	6.99	5.27	13 96	13 16
3	13.22	9 87	8 63	6 15	4.64	3.72
4	16.25	11 65	11.68	8.75	4 58	2.90
5	13.03	8.18	2.01	0 83	11.03	7.35
6	19 25	19 43	5 67	4.40	13.56	15 04
Mean	16 16	12 94*	6 66	4.48**	9 50	8 46
SD	3 31	4.79	3.30	2.97	4 16	4 90

component from 8.63 to 6.15 litre $min^{-1} kPa^{-1}$, while the compartmental slope of the abdomen was unchanged. The slope of the mean ventilatory response to carbon dioxide for the group decreased following high thoracic extradural anaesthesia, as a result of a decrease of the rib cage contribution. The abdominal contribution was unchanged (table III).

DISCUSSION

Resting breathing pattern

Carbon dioxide rebreathing increases rib cage movement by increasing activity of the rib cage inspiratory muscles, particularly the parasternal intercostal muscles [8]. Although lumbar extradural anaesthesia with lignocaine increases the hypercapnic ventilatory response (HVR) by direct action on the respiratory centre [9], high thoracic extradural anaesthesia might impair ventilation if parasternal intercostal muscles are blocked.

We observed a significant change in breathing pattern, namely decreases in *T*I and *T*T and an increase in *V*T/*T*I, following thoracic extradural anaesthesia. *T*E and *V*T also decreased, but not significantly. Consequently $\dot{V}$I increased significantly, although PE'_{CO_2} was unchanged, suggesting an increase in deadspace ventilation. It has been shown that *V*T/*T*I is related closely to central inspiratory activity, while *T*I/*T*T represents respiratory timing in normal humans in whom the inspiratory volume–time relationship is linear [10]. Because PE'_{CO_2} remains unchanged, the observed increase in *V*T/*T*I following extradural anaesthesia indicates an increased central neural drive which may be related to a number of factors. Emotional stress caused by the extradural block could have changed the breathing pattern through cortical influences. The central nervous system (CNS) stimulating effect of lignocaine could also contribute [11]. The excitatory action of lignocaine on the CNS has been reported by several authors. Lignocaine selectively blocks inhibitory neurones in the midbrain reticular formation of the rat, thus facilitating spontaneous neuronal discharge in those neurones under strong inhibitory control [12]. de Jong and colleagues reported enhanced spinal monosynaptic transmission following i.v. lignocaine [13]. The relevance of these findings to our results is not entirely certain, but a facilitatory effect of lignocaine on CNS activity could be one of the causes of the observed increase in neural drive.

The contribution of the rib cage to tidal breathing (*V*rc/*V*T%) in our subjects under resting conditions was comparable to the values reported previously [14, 15]. Following thoracic extradural anaesthesia, *V*rc/*V*T% decreased by approximately 40% in our subjects. This reduction probably reflects decreased activity in the rib cage inspiratory muscles. However, EMG activities of the parasternal intercostal muscles and other inspiratory muscles were not measured and hence any change in their activity cannot be confirmed.

Two possibilities may explain the reduction of *V*rc following extradural anaesthesia. First, because control mechanisms in the spinal cord which govern the intercostal muscles are more susceptible to anaesthetics and neuromuscular blockers than those of the diaphragm, it is reasonable to assume that the efferent traffic to the parasternal intercostal muscles was reduced by the lignocaine administered extradurally. Although Bromage has reported that intensity of motor block with plain lignocaine is negligible regardless of the concentration [16], the concentration used may reduce motor activity of the intercostal muscles. Second, the reduction of *V*rc may have resulted from a reduction of afferent traffic in the intercostal nerves. The discharge of inspiratory intercostal muscle spindles increases during inspiration because of increased fusimotor activity and may reinforce inspiratory motor discharge [4]. A sustained stimulation of chest wall mechanoreceptors has been shown to provoke a slowing of breathing frequency [3], and afferent impulses arising from intercostal muscles can modify the breathing pattern by a decrease of *T*I and *V*T after thoracic dorsal rhizotomy in cats [5]. Extradural anaesthesia may also eliminate these afferent impulses, resulting in the observed changes in breathing pattern.

Hypercapnic ventilatory response

HVR decreased in our study following extradural anaesthesia, in contrast with observations of an increase following lumbar extradural anaesthesia [9], which was suggested to result from a central effect of the lignocaine. However, high thoracic extradural anaesthesia decreased rib cage motion during tidal breathing at rest and during rebreathing to an extent that may have overcome the central stimulant effect of lignocaine. This was confirmed by the observation that $\dot{V}$I,rc/PE'_{CO_2} decreased, while $\dot{V}$I,ab/PE'_{CO_2} was unchanged.

The largest reductions in $\dot{V}\text{I,rc}/P\text{E}'_{CO_2}$ were found in subjects 1 and 5, who had the most extensive extradural block, which also supports this theory. It is of interest that the ventilatory depressant effect of halothane is also explained partially by its action on the rib cage. Tusiewicz and colleagues examined the effect of halothane on HVR and its partitioning into rib cage and abdominal components in human subjects [17] and found a significant decrease of HVR, mainly because of a decrease in the rib cage contribution, during halothane anaesthesia. These findings, together with those of the present study, suggest that mechanical impairment of the rib cage muscles, whatever the cause, can significantly influence the breathing pattern and decrease HVR in healthy human volunteers. However, the central chemoreceptor drive produced by a change in carbon dioxide concentration is not developed fully in the short time required to perform the Read rebreathing technique. Thus if the diaphragm is capable of functioning normally, adequate ventilation should be maintained even with a reduction of the thoracic component of ventilation, after the full hypercapnic drive has developed. On the other hand, if diaphragmatic function is severely impaired, high thoracic extradural anaesthesia could produce ventilatory failure.

We conclude that thoracic extradural anaesthesia may be applied relatively safely to patients with normal diaphragmatic function, but may augment the likelihood of hypoventilation in patients with ventilatory muscle fatigue such as those with severe chronic obstructive pulmonary disease.

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EXTRADURAL PRESSURE FOLLOWING THE INJECTION OF TWO VOLUMES OF BUPIVACAINE

D. L. PAUL AND J. A. W. WILDSMITH

The factors which determine accurately the spread of local anaesthetic in the extradural space have not been fully elucidated. The dose of drug injected [1], patient age [2], arteriosclerosis [3] and pregnancy [2, 4] have been suggested as dominant factors, with lesser contributions from speed of injection [5], direction of needle bevel [6] and patient position [2, 7]. However, the first three of these factors have been disputed [8, 9]. A recent study [10] showed that height of block was independent of dose and volume of solution and unrelated to patient height, weight and age. Another factor said to influence extradural spread, and also to be related to patient age, is the pressure generated by the injection [11]. This led us to re-examine the relationship between the pressure generated by the extradural injection of local anaesthetic solution and the spread of block.

SUMMARY

We investigated the influence of the pressure generated by low lumbar extradural injection of bupivacaine on the development of block in a randomized double-blind study. Thirty patients (aged 17–66 yr) received one of two volumes of 0.75% bupivacaine. Group I ($n = 15$) received 10 ml (75 mg) and group II ($n = 15$) 15 ml (112.5 mg). Injection of the larger volume resulted in a greater pressure at the end of injection, but within 1 min this decayed to the same plateau pressure that was produced by the smaller volume. Mean maximum cephalad spread of block was the same in each group (group I, T9.5; group II, T8.4) and there was no correlation between individual level of block and maximum or plateau extradural pressure, or with patient characteristics.

PATIENTS AND METHODS

Thirty healthy patients who were to undergo elective varicose vein surgery under extradural blockade gave informed consent to the study, which had been approved by the Hospital Ethics Committee.

Each patient was premedicated with temazepam 10 mg by mouth 1 h before arrival in the operating theatre. A venous cannula was inserted in the dorsum of a hand, but no fluids or drugs were administered. The patient was placed in the right lateral position on a horizontal operating table. The extradural space was identified using an 18-gauge Tuohy needle and the loss of resistance technique with as small a volume (1–2 ml) of saline as possible. The third lumbar space was used on each occasion and all the blocks were performed by the same anaesthetist. The needle was inserted with the bevel facing cephalad. After identification of the extradural space the hub was connected, via a three-way tap, to a standard pressure transducer (Sensonor S40), amplifier (S&W 8041) and chart recorder (Elcomatic EM-852). Zero was set with the system and extradural space open to atmosphere and calibration was with a 40-cm water column.

A syringe was attached and 0.75% bupivacaine injected at 0.5 ml s^{-1}. At the end of the injection the three-way tap was turned to form a closed system between the extradural space and the transducer. Pressure was recorded from the start of the injection until 90 s after its completion. The patient was turned supine with a slightly head-down tilt to maintain venous return.

The patients were randomly allocated to receive either 0.75% bupivacaine 10 ml (group I,

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TABLE I. *Demographic data (mean (SD)) for two groups of patients who received extradural block with 0.75% bupivacaine 10 ml (group I) or 15 ml (group II)*

	Group I ($n = 15$)	Group II ($n = 15$)
Age (yr)	42.3 (13.3)	49.3 (11.5)
Sex (M/F)	4/11	5/10
Height (m)	1.70 (0.10)	1.70 (0.10)
Weight (kg)	67.4 (16.3)	66.0 (9.5)
Body mass index (wt ht^{-2})	23.5 (5.8)	22.8 (2.7)

TABLE II. *Extradural pressure data (cm H_2O) (mean (SD) [range]) for two groups of patients who received extradural block with 0.75% bupivacaine 10 ml (group I) or 15 ml (group II).* *$P < 0.05$; **$P < 0.001$

Pressure	Group I ($n = 15$)		Group II ($n = 15$)
Maximum	40.3 (14.5)	*	52.9 (14.2)
(end of injection)	[21.0–67.3]		[30.5–75.9]
Plateau (1 min)	17.9 (7.8)		18.1 (5.4)
	[7.6–34.2]		[11.4–27.0]
Oscillation	6.3 (3.7)	**	13.4 (8.6)
(circulatory impulse)	[1.7–14.6]		[3.8–34.9]

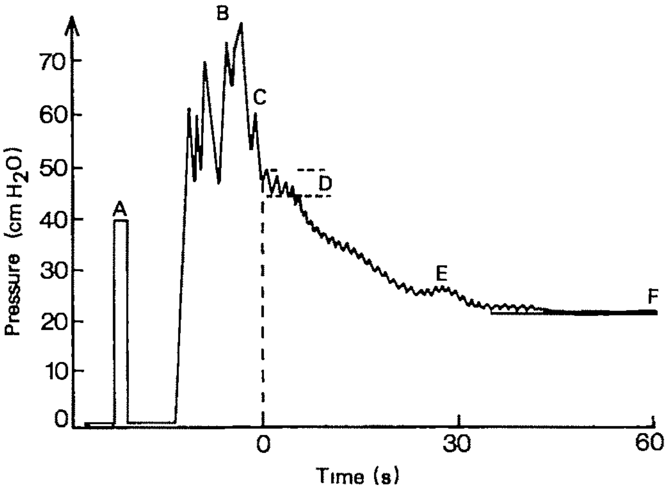

FIG. 1. Sample recording of extradural pressure during and after injection of 0.75% bupivacaine 10 ml. A = Calibration; B = injection artefact; C = end of injection; D = oscillation pressure; E = respiratory artefact; F = plateau pressure.

$n = 15$) or 0.75% bupivacaine 15 ml (group II, $n = 15$). The resulting block was assessed by a single observer who did not know which volume had been injected. The level of sensory block (analgesia to pinprick with a short-bevel 26-gauge needle) and degree of motor block (Bromage score) were assessed at 10-min intervals for 30 min. The patients were sedated lightly (i.v. midazolam) during surgery, for which conditions were adequate in all.

Association of upper level of sensory block with individual patient variables was evaluated by Spearman rank correlation. Comparisons between the two were assessed by the Mann–Whitney test.

RESULTS

There were no significant differences between demographic data for the two groups (table I).

Mean extradural pressure (table II) at the end

TABLE III. *Distribution of block (mean (SD)) in two groups of patients who received extradural block with 0.75% bupivacaine 10 ml (group I) or 15 ml (group II)*

Mean block	Group I	Group II
Sensory (dermatome)		
10 min	L2 8 (5 3)	L2 9 (3.4)
20 min	T11.7 (4.5)	T9.2 (3.5)
30 min	T9.5 (3.1)	T8 4 (3.6)
Motor (Bromage)		
30 min	0 6	0 8

of the injection was greater in group II (52.9 cm H_2O) than in group 1 (40.3 cm H_2O). The range of end injection pressure was wide in both groups (group I, 21.0–67.3 cm H_2O; group II, 30.5–75.9 cm H_2O). Extradural pressure decreased rapidly in both groups and plateaued in every patient within 1 min of the end of injection. There was no difference in mean plateau pressure between the groups. A trace of a sample recording is shown in figure 1. In all patients it was possible to see respiratory and circulatory oscillations superimposed on the extradural pressure trace. These became less marked as the pressure decreased towards the plateau value. The degree of circulatory oscillation was measured immediately after the injection and the mean value was twice as high in group II (13.4 cm H_2O) as in group I (6.3 cm H_2O).

The mean height of block was the same in each group (table III). Full analgesia of the sacral segments was obtained, there were no "missed segments" and all blocks were suitable for the proposed surgery. The degree of motor block was similar in the two groups, most patients being unable to straight-leg raise, but able to extend the knees.

There was no significant correlation between cephalad spread of block and extradural pressure at any time (fig. 2), and no relationship between extent of block and patient age, height, weight or body mass index.

DISCUSSION

These results conflict with the work of Usubiaga [11] who found that the extent of block did relate to generated extradural pressure. Usubiaga injected 2% lignocaine 10 ml through a needle, but

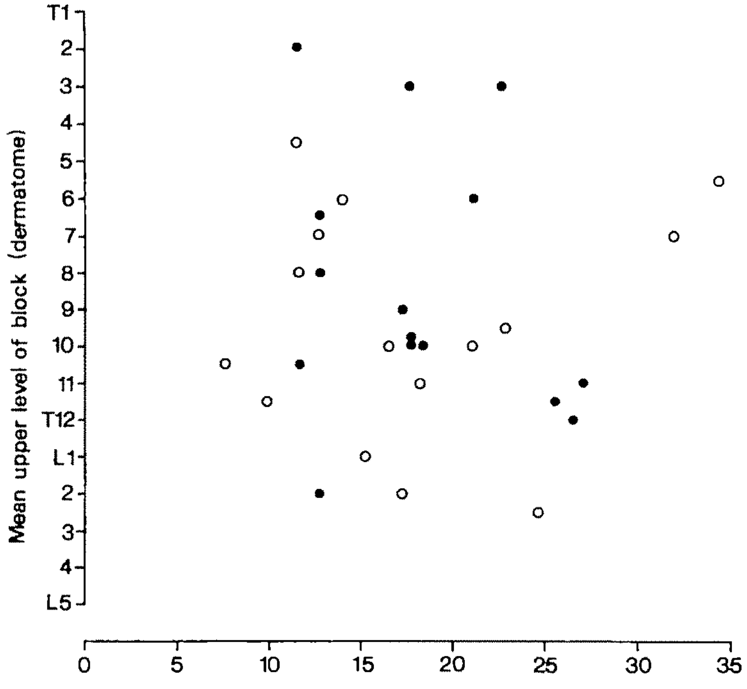

FIG. 2. Relationship between plateau extradural pressure and maximum upper level of block in 30 patients. ○ = 0 75% bupivacaine 10 ml; ● = 0.75% bupivacaine 15 ml.

a catheter was inserted after measurement of pressure and the block was assessed for only 10 min. It is recognized today that a considerably longer period is needed to establish the maximum height of block, although we found no correlation between pressure and block height at any time. It is possible that lignocaine and bupivacaine behave differently or that catheter insertion has some unrecognized influence.

The mean height of block was virtually the same in our two groups, despite a difference of 50% in both volume and dose of bupivacaine injected. This confirms the results of a recent study which also used a "single-shot" technique and examined the independent effects of concentration, volume and dose [10]. The reasons for this further conflict with traditional views are not clear, but also may relate to the use of a catheter in most earlier work.

The pressures measured in the extradural space were very variable, but were significantly greater at the end of the injection of the larger volume. Despite this, the pressures in both groups decreased to the same value in less than 1 min. The oscillation pressures associated with circulatory events were also initially greater after injection of the larger volume. This indicates that the extradural pressure was on a steeper part of the compliance curve than after the smaller injection. An analogy may be made with an oedematous brain within a rigid skull [12], although the "rigidity" of the extradural space would depend as much on the softer tissues as on the bony components of the spinal canal. Bearing this rigidity in mind, it is possible to relate the results of this study to the sequence of events that occurs after injection.

The contents of the canal are to some extent compressible and there are a number of avenues (in theory at least) through which the solution may escape. As local anaesthetic is injected into the extradural space, the volume that it occupies is created by displacement of blood from the venous plexuses and movement of CSF headwards. There may also be some "slack" in the ligaments between vertebrae. Thus the injection of small volumes is likely to produce little or no change in pressure. With the injection of larger volumes, the pressure starts to increase as the capacitance remaining within the system diminishes. This implies that the pressure–volume relationship was not linear, as did the differences between our groups in their initial oscillation pressures. Presumably, the volume at which the pressure starts to increase depends on the characteristics of the individual spinal canal which, in turn, depend on the degree of hydration, venous engorgement, CSF pressure and ligamentous calcification.

The pressure generated during injection causes the local anaesthetic solution to spread out along those tissue planes that offer least resistance. At this stage, there might be some relationship between pressure and spread, but for the potential "leakiness" of the spinal canal. Local anaesthetic might leave the extradural space by absorption into the circulation, diffusion into tissues and escape through the intervertebral foramina, or even along the needle track. The higher the pressure, the quicker this may occur, so leaving proportionately less anaesthetic in the space.

It is interesting that, regardless of the pressure at the end of injection, mean plateau pressure was the same in both groups. This implies that there is a pressure-limiting feature in the extradural space and traditional thinking would probably ascribe this to resistance to fluid escaping through the intervertebral foramina. However, it should be noted that the plateau pressure was at the upper limit of normal for CSF pressure in the lateral position. It may be that displacement of CSF is in fact the main "safety valve" limiting extradural pressure, because recent anatomical studies in cadavers have suggested that solution cannot escape through the foramina [13]. Such a view is supported by a report [14] of sustained increases in ICP after lumbar extradural injection in patients with intracranial space-occupying lesions.

Both the cadaver and the patient with intracranial hypertension may be irrelevant to the clinical situation, and further investigation is needed. The measurement of extradural pressure for a longer period of time might have been helpful, but would have required the use of a catheter, which we wished to avoid. The catheter might modify the direction in which the fluid spreads immediately after injection, or prevent solution leaking along the needle track as could have happened in our subjects.

This analysis might explain why it is impossible to predict height of block from any of a range of readily made measurements and explain our inability, under the conditions of this study, to find any correlation between cephalad spread of block and patient age, height, weight, body mass index or maximum or plateau extradural pressure.

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DOXACURIUM CHLORIDE: A PRELIMINARY CLINICAL TRIAL

R. P. F. SCOTT AND J. NORMAN

SUMMARY

The onset, duration of action and reversibility of doxacurium were studied in 27 anaesthetized patients, using doses of 37.5 µg kg^{-1} (1.5 × ED$_{95}$) and 62.5 µg kg^{-1} (2.5 × ED$_{95}$). Onset was slow and, whilst tracheal intubation was always possible 3 or 4 min after injection, the conditions were not ideal. With the higher dose a mean 97.6 (SD 5.2)% block of the response of adductor pollicis to ulnar nerve stimulation was obtained in 9.85 (6.17) min and recovery of the integrated EMG response to 20% of control took 102 min (42 min). After these initial doses, when incremental doses were given there was no sign of cumulation of effect. Antagonism of block with edrophonium 1 mg kg^{-1}, whilst fast in onset, was rarely complete; with neostigmine 50 µg kg^{-1} antagonism was satisfactory. No adverse haemodynamic effect was seen, although a gradual onset of bradycardia, which responded to atropine or glycopyrrolate, was noted in 12 of the patients. No histamine release or other adverse effects were noted.

Doxacurium, in common with atracurium, is a benzylisoquinolinium, non-depolarizing neuromuscular blocking drug containing two quarternary nitrogen groups. Initial clinical studies in the U.S.A. suggest that it is a potent, long acting drug devoid of cardiovascular and histamine releasing side effects at clinically effective doses [1, 2]. The ED$_{95}$ dose to block contraction of the adductor pollicis muscle is approximately 25 µg kg^{-1} [1]. Unlike atracurium, it is not susceptible to Hofmann degradation, and is probably excreted largely unchanged by the kidney.

This study of doxacurium was designed to assess its onset, intubation conditions, effect of multiple increments and ease of antagonism with edrophonium and neostigmine. A preliminary report of this study was presented to the Anaesthetic Research Society.

PATIENTS AND METHODS

We studied 27 ASA I or II adult patients (weights 45–100 kg) scheduled to undergo elective surgery expected to last 120 min. Each gave written informed consent for the study which was also approved by the local Hospital Ethics Committee.

The patients were premedicated with papaveretum 15–20 mg and hyoscine 0.3–0.4 mg i.m. 1 h before surgery. Before induction of anaesthesia the skin over one forearm and the hand was degreased using an alcohol solution. Five silver–silver chloride electrodes were placed, two over the ulnar nerve, one over the mid-point of the distal skin crease at the wrist, one over the palmar aspect of the head of the fifth metacarpal and one over the belly of the adductor pollicis muscle. These were connected to a Datex Relaxograph. Anaesthesia was induced with thiopentone 4–5 mg kg^{-1} i.v. and fentanyl 2–3 µg kg^{-1} i.v.

Neuromuscular monitoring was commenced using a train-of-four stimuli (2 Hz at 20-s intervals) to the ulnar nerve and the gated, rectified and integrated EMG from the adductor pollicis was recorded. The size of the gain setting, supramaximal-stimulus and the stimulus artefact were noted. Anaesthesia was maintained with 66% nitrous oxide in oxygen and the lungs were ventilated artificially to maintain normocapnia. The patients were allocated to three groups of nine and patient order was randomized. Following randomization the first 18 patients studied (and hence the last nine also) were equally divided

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between the three groups. When an initially stable record was obtained, doxacurium 37.5 μg kg^{-1} i.v. (1.5 × ED_{95}) was administered to group A, and 62.5 μg kg^{-1} i.v. (2.5 × ED_{95}) to groups B and C, with the bolus being given either into a continuous infusion or flushed through a cannula with a 5-ml bolus of saline. The bolus was given to coincide with a train-of-four sequence, to give an accurate time mark on the record.

Intubation conditions were assessed by the same investigator (R.S.) each time at 4 min after the administration of doxacurium in groups A and B and at 3 min in group C. The conditions were graded on a scale of 1–4 (excellent, good, poor or not possible) [3].

The onset of block was determined as the time from injection to the appearance of either complete block or the maximum degree of block. Following maximal block, anaesthesia was maintained with nitrous oxide in oxygen plus 0.5% halothane. Additional doses of fentanyl and thiopentone were administered as required. When the first response of the train-of-four (T1) had recovered to 20% of control, a bolus of doxacurium 5 μg kg^{-1} was given; this was repeated when T1 had recovered again to 20%. The duration and degree of block produced by each increment were noted.

At the end of surgery, when T1 had recovered to greater than 10% of control, the residual block was antagonized with edrophonium 1 mg kg^{-1} i.v. in the first 18 patients (six in each of groups A, B and C), and neostigmine 50 μg kg^{-1} i.v. in the last nine patients ($n = 3$ in each group). Glycopyrrolate or atropine i.v. in an appropriate dose was given concurrently. The percentage recovery of T1 following the injection of the anticholinesterase agent was continuously recorded.

Heart rate was observed continuously from a Hewlett–Packard ECG monitor and the arterial pressure measured every 2 min using a Hewlett–Packard non-invasive monitor. To minimize decreases in core and hand temperatures during the operation, nasopharyngeal temperature was measured, all infusions were warmed to body temperature, a condenser humidifier was used in the breathing system and the forearm was insulated by wrapping in towelling.

Neuromuscular monitoring was stopped when the patient was awake, and neuromuscular function was evaluated clinically during the recovery period by assessing patient's grip strength and ability to head lift for 5 s [4]. Each patient was reassessed 24–48 h after surgery and questioned with regard to any adverse experience noted.

Non-parametric and Student's *t* test were used as appropriate to assess statistical significance.

RESULTS

There were no significant differences between the ages, weights or ASA groups of the three groups of patients studied (table I). The duration of surgery was defined as the time from administration of the initial bolus of doxacurium until administration of the antagonizing agent. Intubation conditions ranged between grades excellent and poor in all three groups, but only one patient in each group achieved excellent conditions (table II). Intubation was accomplished successfully in all patients, although 100% block of adductor pollicis was not achieved before intubation was performed.

Because patients in groups B and C all received doxacurium 62.5 μg kg^{-1}, these two groups were analysed together and compared with group A

TABLE I. *Patient characteristics (mean (SD))*

	n	Age (yr)	Weight (kg)	Duration of surgery (min)	Sex (M/F)
Group A Doxacurium 37.5 μg kg^{-1}	9	52.5 (11.8)	67.3 (10 7)	127 8 (58.4)	5/4
Group B Doxacurium 62.5 μg kg^{-1}	9	60.7 (11 2)	69 8 (15 8)	161.4 (48.6)	7/2
Group C Doxacurium 62 5 μg kg^{-1}	9	49 (14 0)	74.5 (15.0)	139.6 (38.7)	6/3

TABLE II. *Intubation data. Score 1 = excellent, 2 = good; 3 = poor; 4 = not possible*

	Time of intubation (min)	Intubation score (No. patients)						Reduction in T1 at intubation (%)
		1	2	2.5	3	4	Mean (SD)	
Group A Doxacurium 37.5 µg kg^{-1}	4	1	4	1	3	0	2.27 (0.66)	55.2 (32.9)
Group B Doxacurium 62.5 µg kg^{-1}	4	1	6	1	1	0	2.0 (0.5)	80.1 (15.5)
Group C Doxacurium 62.5 µg kg^{-1}	3	1	6	0	2	0	2.1 (0.6)	67.1 (26.0)

(doxacurium 37.5 µg kg^{-1}) (table III). Three patients in group A failed to achieve 80% block following the initial bolus and one patient was antagonized at 10% recovery. In the remaining five it took an average of 51 min to recover to T1 of 20%. With the higher dose, in one patient the initial block was only to 75%, and in two the recording was lost following movement of the patient by theatre staff and loss of electrode placement. In the remaining 15, the time to 20% T1 recovery was on average 102 min after the initial dose (table III). There was no significant correlation between the age of the patients and duration of block at this higher dose.

Only 13 patients received increments of doxacurium as, in the remainder, the initial bolus dose of doxacurium was adequate to last throughout the operation. The incremental doses administered at 20% recovery of T1 produced a moderately wide between-patient variation in response, both with regard to percent increase in block of T1 and time to return to 20% T1. However, the response in any one patient was consistent, with increments producing the same increase in paralysis and a constant duration of effect (table IV).

Two patients with poor recovery recordings were omitted from the antagonism data analysis. The mean percent recovery of T1 at the time of administration of the antagonist was almost the same in the edrophonium and neostigmine groups (table V). The first twitch of the train-of-four was antagonized well after neostigmine. The T1 antagonism response to edrophonium was rapid

TABLE III. *Onset and duration data (mean (SD) [range]). *Three patients failed to achieve 80% block*

	n	Max. block achieved (T1%)	Time to max. block (min)	Duration to 20% recovery of T1 (min)
Group A Doxacurium 37.5 µg kg^{-1}	9	83.6 (18.3) [55–100]	10.5 (2.2) [6–14]	N/A*
Groups B+C Doxacurium 62.5 µg kg^{-1}	18	97.6 (5.2) [78–100]	9.85 (6.17) [5–31]	101.7 (41.8) [31–175] (*n* = 15)

TABLE IV. *Response to increments (5 µg kg^{-1}) (mean (SD) [range]), †Group A* n = *4; group B* n = *4; group C* n = *5*

No. patients receiving increments at 20% recovery T1		Increase in block T1 (%)	Duration to return to 20% (min)	No. increments
Total	13†	8 (3.3) [2.5–15]	31.3 (31.1) [9.5–42]	3.9 (3.8) [1–12]

TABLE V. *Data on antagonism of block by edrophonium or neostigmine (mean (SD) [range])*

		Recovery of T1 (%) at				
	n	Drug admin.	1 min	3 min	5 min	10 min
Edrophonium	17	23.8 (8.8) [10–37]	59.2 (22.8)	70.9 (17.3)	76.4 (17.4)	78.0 (16.7)
Neostigmine	8	22.5 (6.7) [10–32.5]	40.6 (21.2)	70.5 (28.2)	81.8 (21.0)	94.3 (12.2)

in onset but was incomplete and subsequently appeared to be similar to that of a spontaneous recovery. In eight (47%) patients in the edrophonium group a train-of-four (TOF) ratio less than 0.5 was still present when recording had to be stopped. Only four (24%) patients achieved a TOF ratio greater than 0.7. One patient, with a TOF ratio of 0.6 at the end of recording, failed a 5-s head lift 30 min after administration of edrophonium. Ten minutes later he had a successful head lift following administration of neostigmine 2.5 mg. In the neostigmine group, no neuromuscular block could be detected by clinical assessment in the recovery room. One patient had a train-of-four ratio less than 0.5 following antagonism at the end of the recording. Four patients (50%) achieved a TOF ratio greater than 0.7. The mean period of recording following administration of both agents was approximately 14 min.

Twelve (44.4%) patients required administration of an i.v. anticholinergic agent during operation to correct a heart rate of less than 50 beat min^{-1}.

The bradycardias were gradual in onset and generally occurred 30–60 min after induction of anaesthesia and seemed unrelated to the administration of doxacurium.

No adverse experiences were reported by the patients on follow-up at 24 h.

DISCUSSION

This study confirms that doxacurium is a potent, long acting neuromuscular blocking agent. Although a formal dose–response study was not carried out in our patients the drug appeared to be less potent than might have been anticipated from previous reports. Other studies [1, 2, 5, 6] suggest that the ED_{95} lies between 13.6 and 25 μg kg^{-1}, depending on the anaesthetic conditions. The dose regimen in this study was based on the initial report by Basta and colleagues which suggested the ED_{95} under balanced anaesthesia was 25 μg kg^{-1} [1]. In our study, group A received 1.5 times this ED_{95} and groups B and C received 2.5 times the ED_{95}. Our data, however, showed that at 37.5 μg kg^{-1} (1.5 × ED_{95}) the maximum block achieved was 83.6% T1. This apparent difference in potency may result from the fact that we compared EMG responses to mechanomyographic forms of measurement [1, 2]. In addition, the drug may appear less potent because of the lighter depth of anaesthesia during induction. Alternatively, there may be an Anglo–American difference in potency for doxacurium, as had been described previously for tubocurarine [7].

Intubating conditions were similar to those described by other workers [8, 9] and could only be described as excellent in one patient in each group; in no patient was 100% blockade of T1 achieved before intubation. In two patients the intubating conditions were between grades 2 and 3 by the intubation criteria of Twohig and his colleagues [3] and therefore they scored 2.5. Even at the high dose (62.5 μg kg^{-1}) the mean onset time to 90% block of T1 was some 4.9 min ($n = 17$). Nevertheless, in no patient was intubation impossible and the mean conditions in all three groups could be said to be good.

In the patients receiving multiple maintenance increments of doxacurium there was no evidence of an increase in duration or degree of block following each bolus.

In all patients except the two with poor recordings, in whom antagonism was blind, the block was antagonized between 10 and 37% recovery of T1. It could be argued that the poor antagonism with edrophonium was related to baseline drift of the electromyographic recording, which has been well documented by other authors [10, 11]. However, the antagonism of T1 by neostigmine was complete; this would confirm a real difference in ability to antagonize doxacurium by these two anticholinesterase agents. As a result of time constraints imposed on this clinical study, TOF fade was still present in several patients when stimulation had to be stopped as the patient awakened. Nevertheless, with the exception of one patient who received edrophonium, all other patients appeared to have appropriate clinical antagonism of block and had satisfactory grip strength and 5-s head lift when tested between 20 and 40 min after admission to the recovery ward.

It is unlikely that the gradual onset of bradycardia could be attributed to doxacurium; our measurements of heart rate and arterial pressure confirm the findings of others that doxacurium is a haemodynamically stable agent [1, 12]. There was no clinical evidence of histamine release. Konstadt also noted a decrease in heart rate and attributed this to progressive reduction in sympathetic tone resulting from anaesthesia [13]. The effect of opioids and volatile agents on heart rate is well documented [14].

In conclusion, we found doxacurium to be a potent, long acting, haemodynamically stable, non-depolarizing neuromuscular blocker. Although intubation was possible in all patients in the three groups studied and with the doses used in this study, doxacurium did not provide intubating conditions which could be described as excellent. In common with vecuronium and atracurium, this drug does not have the protective vagolytic effect of pancuronium and it is recommended that an anticholinergic agent be available immediately if vagal stimuli are likely to be encountered during surgery. Neostigmine would appear to be more suitable than edrophonium as an antagonist for doxacurium.

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LUNG FUNCTION IN THE SUPINE AND LATERAL DECUBITUS POSITIONS IN ANAESTHETIZED INFANTS AND CHILDREN†

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SUMMARY

We have measured dynamic lung compliance or static lung thorax compliance, functional residual capacity (FRC), and two indices of pulmonary gas mixing (pulmonary clearance delay (PCD) and single breath alveolar mixing efficiency (SBAME)) in 25 children in the supine and lateral decubitus position during nitrous oxide–halothane anaesthesia. Fifteen children (5 month–8 yr) breathed spontaneously and 10 (4 month–9 yr) underwent mechanical ventilation. Tidal volume and rate of ventilation were, respectively, 3.5–6.6 ml kg^{-1} and 22–46 b.p.m. in spontaneously breathing supine children, and 8.3–15 ml kg^{-1} and 20–30 b.p.m. in mechanically ventilated supine children, and did not differ significantly in the lateral position. There was no significant change in compliance when the child was turned to the lateral position, but FRC increased from 22 (SD 7) to 25 (8) ml kg^{-1} ($P < 0.01$) in the spontaneously breathing group and from 19 (6) to 24 (8) ml kg^{-1} ($P < 0.01$) in the other group. In spontaneously breathing children, PCD and SBAME indicated a somewhat impaired pulmonary gas mixing ($P < 0.05$) after the child had been turned to the lateral position, but no change occurred in the other group. These findings suggest that the distribution of ventilation in anaesthetized children in the lateral position is similar to that reported previously in anaesthetized adults.

In awake adults who assume the lateral position, the upper lung increases in volume but the greater fraction of ventilation goes to the lower lung, the volume of which decreases slightly. The result is a moderate increase in functional residual capacity (FRC) and an uneven pulmonary gas mixing as measured by the nitrogen washout technique [1, 2]. Based on studies in infants with known or suspected pulmonary diseases, it has been suggested that children may exhibit a "reversal of adult pattern" in respect of pulmonary gas distribution [3], but no systematic studies have been undertaken in anaesthetized children with healthy lungs. To test if children differ from adults, we have studied the effects of the lateral position on compliance, FRC and the washout of an insoluble gas in children during spontaneous breathing and mechanical ventilation.

PATIENTS AND METHODS

Twenty-five infants and children, aged 4 months to 9 yr, were studied. Fifteen children (table I) were undergoing abdominal or urogenital surgery and breathed spontaneously. Ten children (table II) were undergoing abdominal surgery or surgery for aortic coarctation involving mechanical ventilation. All children were free from respiratory disease and the two groups were similar in respect of age, weight and height. Compliance and FRC in children with aortic coarctation (patients Nos 21–25, table II) have been reported previously [4]. Parental consent was obtained and the study was approved by the local Human Studies Committee.

Patients older than 1 yr received a mixture of diazepam 0.5 mg kg^{-1}, morphine 0.15 mg kg^{-1}, and hyoscine 0.01 mg kg^{-1}, rectally 1 h before induction of anaesthesia. Infants (younger than

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TABLE I. *Spontaneously breathing children* (n = *15*). *Demographic data and results. S = Supine position; L = left lateral position. PCD = pulmonary clearance delay* [*7*]; *SBAME = single breath alveolar mixing efficiency* [*8*]. $^*P < 0.05$; $^{**}P < 0.01$; *ns = not significant*

Patient No.	Age (month)	Weight (kg)	Height (cm)	Vent. rate (b.p.m.)		V_T (ml kg^{-1})		C_L (ml cm H_2O kg^{-1})		FRC (ml kg^{-1})		PCD (%)		SBAME (%)	
				S	L	S	L	S	L	S	L	S	L	S	L
1	5	6.5	63	44	43	3.5	3.4	—	—	13	12	17	51	79	86
2	6	7.6	69	45	44	4.3	4.1	0.7	1.3	15	17	33	25	86	84
3	7	8.4	63	44	46	3.5	3.2	1.3	2.5	18	19	10	18	92	90
4	9	9.7	74	44	45	4.8	4.9	1.0	0.9	16	21	—	—	93	91
5	10	9.7	73	37	36	5.5	5.4	—	—	14	15	14	23	88	82
6	21	11	82	33	38	4.1	3.5	1.1	0.9	14	15	22	23	84	76
7	29	15	94	43	45	3.7	3.9	2.5	1.8	21	25	31	33	83	84
8	37	12	89	44	45	6.6	5.5	—	—	30	34	23	28	90	87
9	51	18	109	23	23	5.8	5.6	0.6	1.6	31	35	31	28	91	90
10	61	18	109	29	31	4.3	3.7	—	—	32	38	27	53	87	72
11	67	20	109	35	24	4.2	3.8	0.7	0.9	29	29	34	51	74	72
12	77	28	124	29	29	4.0	4.0	1.0	1.0	19	27	21	23	85	82
13	78	21	116	22	22	4.8	4.7	1.5	1.8	31	33	31	28	90	91
14	85	25	123	27	28	4.0	3.9	1.1	1.1	28	33	21	33	91	74
15	94	23	123	28	27	4.5	4.7	1.0	1.0	24	28	30	26	87	88
Mean	42	16	95	35	35	4.5	4.3	1.1	1.3	22	25	25	32	87	83
SD	32	7	23	8	9	0.9	0.8	0.5	0.5	7	8	8	12	5	7
				ns		ns		ns		**		*		*	

TABLE II. *Mechanically ventilated children* (n = *10*). *Demographic data and results. Ventilatory settings were the same in both positions. S = Supine position; L = lateral position. Patients Nos 16–20 were placed in the left lateral, the others in the right lateral position. PCD = pulmonary clearance delay* [*7*]; *SBAME = single breath alveolar mixing efficiency* [*8*]. $^{**}P < 0.01$; *ns = not significant*

Patient No.	Age (month)	Weight (kg)	Height (cm)	Vent. rate (b.p.m.)	V_T (ml kg^{-1})	C_{Lt} (ml cm H_2O kg^{-1})		FRC (ml kg^{-1})		PCD (%)		SBAME (%)	
						S	L	S	L	S	L	S	L
16	4	4.9	63	25	12	—	—	14	16	45	30	91	93
17	6	8.2	69	20	15	0.7	0.6	13	17	23	25	90	87
18	27	12	82	20	8.3	0.7	0.7	15	16	21	12	91	95
19	33	14	94	20	13	1.0	1.1	25	31	26	25	90	92
20	43	18	101	20	10	1.0	1.0	20	28	22	17	94	96
21	11	9.6	76	30	11	0.6	0.9	11	18	23	28	93	87
22	20	13	83	27	8.5	0.9	0.7	18	19	29	30	90	97
23	61	19	112	21	9.7	1.2	1.0	31	37	17	14	92	92
24	81	23	120	21	10	1.0	1.0	24	29	18	19	97	90
25	114	33	137	20	8.7	0.8	0.8	21	25	22	29	96	95
Mean	40	15	94	22	11	0.9	0.9	19	24	25	23	92	92
SD	37	8	24	4	2	0.2	0.2	6	8	8	7	3	4
						ns		**		ns		ns	

1 yr) received no premedication. Anaesthesia was induced with i.v. thiopentone (*n* = 19) or halothane (*n* = 6). Intubation was facilitated with suxamethonium in 20 children and the trachea was intubated with a cuffed tracheal tube (Mallinckrodt or Portex). The cuff was inflated during measurements. Anaesthesia was maintained with 1% halothane and 50–70% nitrous oxide in oxygen. In spontaneously breathing children a Mapleson D system was used with a fresh gas flow three times the estimated ventilation. In 12 of these 15 children anaesthesia was supplemented with a caudal block using 0.25% bupivacaine 0.5 ml kg^{-1}. In the second group of children,

undergoing mechanical ventilation, vecuronium 0.1 mg kg^{-1} or alcuronium bromide 0.25 mg kg^{-1} was given to maintain muscle paralysis during measurements. Ventilation was controlled using a Servo ventilator 900C (Siemens–Elema) at 20–30 b.p.m. Positive end-expiratory pressure was not used. The tidal volume was adjusted to give an end-tidal $P\text{CO}_2$ of 4–5 kPa and the ventilator was set at constant inflation flow. The inflation time was 25 or 33 % and end-inspiratory pause time was 0 or 10% of the cycle of ventilation. The pattern of ventilation was unchanged in each child during all measurements, except during measurement of compliance, when a 10% end-inspiratory pause was used in all children.

Measurements

Measurements were made after induction of anaesthesia but before surgery. At least 15 min of halothane administration had elapsed before the first set of measurements. Airway flow, oesophageal pressure (*P*oe), airway (mouth) pressure *P*m), and FRC were measured with patients in the supine position and in the lateral decubitus position with the upper arm placed over the head. In the spontaneously breathing group all children were turned to the left side and measurements were made in the following order: supine–left lateral–supine ($n = 7$); supine–left lateral ($n = 4$); and left lateral–supine ($n = 4$). In the group undergoing mechanical ventilation, measurements were made with patients first in the supine position and then in the left lateral (Nos 16–20) or right lateral position (Nos 21–25). In this group, duplicate FRC determinations were made in both positions.

The measurement system is shown in figure 1. In spontaneously breathing children the apparatus deadspace was 8 ml in children less than 10 kg in weight, and 12 ml in children weighing more than 10 kg. In the mechanical ventilation group, apparatus deadspace varied between 8 and 35 ml, because a heat/moisture exchanger was used in some children. Airway flow was measured using a heated Fleisch pneumotachograph No. 00 or 0 (Gould) with a differential pressure transducer (MP 45-1-871, Validyne) or by the standard flowmeter of the ventilator (Nos 21–25). The pneumotachograph signal was zero-adjusted and calibrated before each measurement with a precision pump using 50% nitrous oxide in oxygen. The flowmeter of the ventilator was calibrated against a wet gas meter (Flonic, Schlumberger) during ventilation with 50% nitrous oxide in oxygen. Tidal volume ($V\text{T}$) was obtained by integration of the flow signal.

In spontaneously breathing children, *P*m and

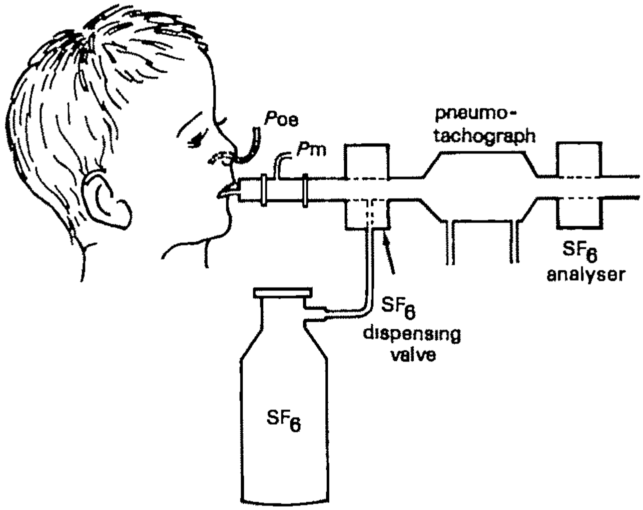

FIG. 1. The set-up during FRC and gas mixing measurements. The apparatus deadspace was 8 ml with a Fleisch pneumotachograph No. 00 and 12 ml with a Fleisch No. 0. The corresponding pressure decreases across the system at a flow of 150 ml s^{-1} were 1 cm H_2O and 0.25 cm H_2O, respectively. DPT = differential pressure transducer. A slightly modified system was used in patients 21–25, in whom the flow signal was obtained from the flowmeter of the ventilator.

Poe were measured at the tracheal tube connection and in mid-oesophagus, respectively, using pressure transducers (PDCR-75, Druck) calibrated at a pressure of -20 cm H_2O. The position and function of the water-filled oesophageal catheter was assessed by occluding the airway at FRC [5]. A ratio of 0.9–1.1 between oesophageal and airway pressure changes at occlusion was considered satisfactory. In mechanically ventilated children Pm was measured in the expiratory tubing with the manometer mounted on the ventilator, as supplied by the manufacturer. The manometer was calibrated against a mercury manometer.

Flow, volume and pressures were recorded on an ink-jet recorder (EM-81, Siemens–Elema) and dynamic lung compliance (CL) was calculated from the tracings as:

$$C\text{L} = V\text{T}/\Delta(P\text{oe} - P\text{m})$$

where VT equals the tidal volume (BTPS), and $\Delta(P\text{oe} - P\text{m})$ the change in pressure during inspiration. The mean value obtained in 10 consecutive breaths was used for the calculations. During mechanical ventilation, breath-by-breath static lung–thorax compliance (CLt) was obtained as:

$$C\text{Lt} = V\text{T}/(P\text{I}' - P\text{E}')$$

where PI$'$ equals the airway pressure at the end of the end-inspiratory pause and PE$'$ the airway pressure at the end of expiration. During compliance measurements the end-inspiratory pause was 0.2–0.3 s. PE$'$ was obtained by noting the pressure in the tubing during an "end-expiratory hold", with both the inspiratory and expiratory valves closed. This function was activated for approximately 1 s. In patients Nos 21–25, in whom airway flow was measured by the flowmeter of the ventilator, compliance of the tubing (0.5 ml/cm H_2O) was subtracted from the obtained value.

FRC was measured with a multiple breath washout technique using sulphur hexafluoride (SF_6) as tracer gas [6]. Tracer gas concentration is measured in the apparatus deadspace with an infra-red transducer placed over a cuvette with windows (fig. 1). SF_6 is washed in through a dispensing device, which mixes SF_6 in proportion to inspiratory flow until a stable and uniform alveolar concentration of approximately 0.5% is attained. SF_6 washout is started by stopping the tracer gas infusion at the end of inspiration and is considered complete when the concentration is less than 0.001%. Signals representing expired flow and SF_6 concentration are fed into a computer (PDP 11/23, Digital Equipment), which calculates FRC as the volume of SF_6 washed out divided by the alveolar concentration at the end of the washin period. The value obtained is converted to BTPS and apparatus deadspace is subtracted.

Pulmonary clearance delay (PCD) was calculated as described by Fowler and colleagues [7]. The index compares the average time that a tracer gas molecule remains in the lungs (T_1) with the average time that a tracer gas molecule would remain in a uniformly ventilated lung with the same FRC, series deadspace and tidal volume, before being expired (T_2). PCD is obtained as:

$$100 \times (T_1 - T_2)/T_2$$

The average time that a tracer gas molecule remains in the lungs is calculated from the washout curve. Calculation of PCD was with an interactive computer program which approximated the curve as the sum of exponentially decaying functions: the computer plotted the washout curve semilogarithmically, and the user indicated how lines should be drawn in order to obtain the exponential curve components. The "peel-off" method was used, that is, the slowest component was first subtracted and the plot was redrawn to identify the remaining component. In all cases, an adequate approximation of the curve was achieved with two components. Single breath alveolar mixing efficiency (SBAME) was calculated by the method of Cumming and Guyatt [8] as the actual volume of tracer gas in the first expiration during washout expressed as a percentage of the "ideal" volume, had gas mixing in the lungs been perfect. The normal values for awake healthy adults in the supine position in our laboratory are 39 (20)% for PCD and 85 (5)% for SBAME. As far as we know, no studies of PCD have been performed in spontaneously breathing, awake children younger than 8 yr and only one study has reported SBAME in children and young adults 5–20 years of age [9]. In that study, SBAME was obtained from an expiration of TLC to FRC using nitrogen as tracer gas. The mean value was 83%.

Arterial oxygen tension ($P\text{a}_{O_2}$) was measured in the five children who were to undergo corrective surgery for coarctation of the aorta. In the five remaining children undergoing mechanical ventilation, arterial oxygen saturation ($S\text{a}_{O_2}$) was assessed by pulse oximetry.

Statistics

t Test for paired or unpaired data was used when appropriate. Probability values less than 0.05 were considered statistically significant. Regression equations were obtained by the method of least squares. The coefficient of variation for duplicate FRC determinations was obtained as:

$$SD/m = D/m \times \sqrt{2}$$

where D is the absolute value of the difference between the observations and m the mean. Data are given as mean (1 SD) when not otherwise indicated.

RESULTS

The ventilatory rate was greater and the tidal volume smaller in spontaneously breathing children than in the children undergoing mechanical ventilation. In the supine position, FRC was not significantly different in the two groups. The mean value in all patients ($n = 25$) was 21 (7) ml kg^{-1} and the correlation to body weight was: FRC (ml) = $-86+28 \times$ weight (kg), $r = 0.92$. In the supine position, PCD values in the two groups were not significantly different, while SBAME was less during spontaneous breathing than during mechanical ventilation ($P < 0.01$).

Spontaneously breathing children (table I)

The order in which supine and left lateral position measurements were obtained did not affect the result. Therefore, the values presented are mean values of measurements obtained in each position.

There was no significant change in breathing rate or tidal volume between the two positions. In the supine position, breathing rate was 35 (8) b.p.m. and V_T was 4.5 (0.9) ml kg^{-1}. Correlation between V_T and body weight was:

$$V_T \text{ (ml)} = 3.2+4.3 \times \text{weight (kg)},\ r = 0.93$$

Ventilation in the supine position was 184 (53) ml kg^{-1} min^{-1} and the correlation to body weight was:

$$\text{ventilation (ml)} = 1028+77 \times \text{weight (kg)},\ r = 0.74$$

Satisfactory measurements of C_L were obtained in 11 of the 13 children in whom this was attempted. In the remaining two, measurements were discarded because cardiac oscillations made the oesophageal pressure tracings difficult to interpret. C_L supine was 1.1 (0.5) ml kg^{-1} cm H_2O and C_L in the lateral position was 1.3 (0.5) ml kg^{-1} cm H_2O (ns). FRC supine was 22 (7) ml kg^{-1}; it increased by 13% when turned to the lateral position ($P < 0.01$). Both PCD and SBAME indicated significantly more uneven pulmonary gas mixing ($P < 0.05$) when the children were turned to the lateral position. The washout curves obtained in one patient are shown in figure 2.

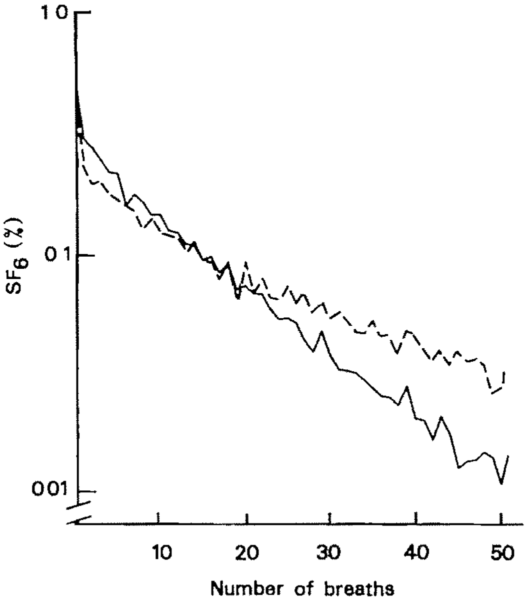

FIG. 2 Patient No. 10: mean SF_6 concentration in each expiration *v.* breath number during washout in the supine (——) and lateral (- - -) position. The corresponding pulmonary gas mixing values are shown in table I.

Mechanical ventilation (table II)

In these children V_T was 11 (2) ml kg^{-1} and ventilation 234 (56) ml kg^{-1} min^{-1}. C_{Lt} was similar in supine and lateral positions (0.9 (0.2) ml cm H_2O kg^{-1}). The median coefficient of variation for duplicate FRC determinations was 1.4% (range 0.8–5.3%) in the supine position and 2.3%, (range 0.9–3.8%) in the lateral position. FRC was 19 (6) ml kg^{-1} in the supine position and 25 (19)% greater ($P < 0.01$) in the lateral position. The increase in FRC was similar in children placed on their left (Nos 16–20) and children placed on their right side (Nos 21–25) (mean increases 24 and 27%, respectively). Neither PCD nor SBAME changed significantly between the supine and lateral position. In the five children

(Nos 21–25) in whom arterial blood was obtained, Pa_{O_2} changed from 23.3 (9.3) kPa supine to 26.7 (9.3) kPa in the lateral position (ns). In the other children (Nos 16–20), Sa_{O_2} was unchanged, at 97 % or greater, after the child had been turned to the lateral position.

DISCUSSION

The first measurements were made when the child had inhaled 1 % halothane for 15 min. Because of the alveolar uptake of halothane, the alveolar concentration during measurements probably varied between 0.6 and 0.7 % [10]. However, this small change in alveolar halothane concentration was not expected to influence the results and there were no significant changes in *C*L, FRC or mixing efficiency with time in the seven spontaneously breathing children in whom supine measurements were obtained both before and after the measurement in the lateral position. Furthermore, preliminary studies indicate that FRC changes little with increasing alveolar halothane concentrations in children with an intubated trachea. In two spontaneously breathing children FRC decreased by 2 % and 4 %, respectively, when the end-tidal halothane concentration was increased from 0.5 to 1.5 %.

The effect of the lateral position has been well documented in anaesthetized adults [2, 11–13]. The changes occurring in ventilation distribution may be explained by the changes in end-expiratory lung volume: anaesthesia reduces FRC and, because of the S-shaped pressure–volume curve, compliance is also commonly reduced compared with the awake state [12]. The lateral position causes expansion of the upper lung and thus improves compliance of that lung [11–14]. Hence, a greater fraction of the tidal volume is distributed towards the upper lung during both spontaneous breathing and mechanical ventilation. In mechanical ventilation in adults, the change in ventilation distribution between the two lungs is proportional to the change in lung volumes; pulmonary gas mixing, as measured by pulmonary clearance delay, therefore remains unchanged. However, in spontaneously breathing adults Rehder and Sessler [12] found that lung clearance ratio, another index of pulmonary gas mixing, increased from 2.8 (0.3) supine to 3.2 (0.2) in the lateral position ($n = 9$), $P < 0.05$), suggesting a mismatch between ventilation and lung volume. The reason for this difference in pulmonary gas mixing between mechanical ventilation and spontaneous breathing may be that the lateral position results in cranial shift and, therefore, in a greater preload of the lower diaphragm. Thus the fraction of ventilation to the lower lung does not decrease as much during spontaneous breathing as during mechanical ventilation. Although double-lumen tubes were not used in the present study, the observed changes in FRC and pulmonary gas mixing efficiency are in accordance with these findings, indicating that the lateral position results in similar changes in lung volume and mechanics in anaesthetized children and adults. Davies and colleagues [3] used krypton-81 m scanning to assess ventilation distribution in the lateral position in 18 children with known or suspected pulmonary disease and they found that ventilation was distributed preferentially towards the upper lung. The patients were not anaesthetized, but three children required ventilatory support and the diagnoses of the remaining children suggest that most breathed at abnormally low lung volumes. These findings may also be explained by the mechanisms outlined above in anaesthetized patients.

The mean compliance values observed in the present study in supine children agree with previous findings in anaesthetized children without pulmonary disease [15]. There are problems associated with inferring the pleural pressure from oesophageal pressure. First, oesophageal pressure may be determined not only by the pleural pressure, but also by mechanical properties of the oesophagus and the pressure in the space surrounding it [16]. Second, because there exists a pleural pressure gradient [17], the oesophageal pressure may at best represent only a regional pleural pressure, which is probably different in the supine and lateral positions. However, studies in adults and in infants indicate that oesophageal pressure reflects *changes* in pleural pressure equally well in the supine and lateral positions if the oesophageal catheter is placed accurately as judged by the occlusion test [5, 18]. In our patients, *C*L in the lateral position was not significantly different from *C*L supine. This may be because a slight increase in compliance of the upper lung was opposed by a slight decrease in compliance of the lower lung. The unchanged compliance and the increased FRC in the lateral position are in contrast to the findings of Helms and colleagues [19] who studied anaesthetized spontaneously breathing children ($n = 9$)

and observed a significant increase in CL, but no change in FRC when turning the child to the lateral position. These authors used a body plethysmograph, and the median age in their series was 7 months, while the median age in our study was 3 yr. Although FRC increased in 13 of 15 spontaneously breathing children in the present study, the mean increase in the five youngest (median age 7 months) was only 9% (ns). The lateral position may thus have a less marked effect in infants, perhaps because of the smaller difference between anterior–posterior and transverse diameters. Also, infants have a compliant chest wall which may cause greater reductions in FRC during anaesthesia [20] and a more marked compression of the lower lung in the lateral position.

Results from two studies in awake children [9, 21] suggest that ventilation may be distributed more unevenly in young children than in adults. This is not supported by the present study in which pulmonary gas mixing in the supine position was generally as good as, or better than, what is commonly observed in healthy adults.

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ALFENTANIL OBTUNDS THE CARDIOVASCULAR AND SYMPATHOADRENAL RESPONSES TO SUXAMETHONIUM-FACILITATED LARYNGOSCOPY AND INTUBATION

B. SCHEININ, M. SCHEININ, J. VUORINEN AND L. LINDGREN

SUMMARY

Alfentanil 75 μg kg^{-1} or saline (control group) was given 1 min before induction of anaesthesia in 20 healthy patients premedicated with diazepam 0.14 mg kg^{-1} and pethidine 1 mg kg^{-1}. Anaesthesia was induced with a sleep dose of thiopentone preceded by glycopyrrolate. Suxamethonium 1 mg kg^{-1} was used to facilitate laryngoscopy (which lasted 10 s) and tracheal intubation. Arterial pressure, heart rate and noradrenaline concentration in mixed venous plasma increased significantly after suxamethonium, and increased further after laryngoscopy and intubation in the control group (n = 10). The QT interval of the ECG was prolonged after the administration of suxamethonium, and was prolonged further after laryngoscopy and intubation. All these changes were attenuated in patients pretreated with alfentanil (n = 10), but four patients had chest wall rigidity. Changes in the QT interval correlated directly with the changes in plasma noradrenaline concentration (r = 0.67). Plasma adrenaline concentrations decreased during induction of anaesthesia in both groups.

Tracheal intubation is associated with increases in arterial pressure, heart rate [1, 2] and plasma catecholamine concentrations [1–9], in addition to prolongation of the QT interval of the ECG and cardiac arrhythmias in some patients [10].

Fentanyl 6 μg kg^{-1} has been found to abolish these cardiovascular responses to intubation [11]. Alfentanil also offers protection against the increases in arterial pressure and heart rate which occur during tracheal intubation [8, 12]. Alfentanil 250 μg kg^{-1} has been given to healthy patients without untoward cardiovascular effects [13], whereas alfentanil 40 μg kg^{-1} caused hypotension and bradycardia in a group of patients, some of whom were receiving β-blockers or other antihypertensive drugs [8].

The aim of the present study was to investigate the cardiovascular and sympathoadrenal responses to suxamethonium-facilitated laryngoscopy and intubation, in addition to the relationship between plasma catecholamine concentrations and ECG changes in healthy patients given either alfentanil 75 μg kg^{-1} or saline before induction of anaesthesia.

PATIENTS AND METHODS

Clinical procedure

The study was approved by the Hospital Ethics Committee and informed consent was obtained from all patients. We studied 20 patients (ASA I) scheduled for elective surgery (table I); patients receiving any drug therapy were excluded from the study.

All patients were premedicated with diazepam 0.14 mg kg^{-1} by mouth and pethidine 1 mg kg^{-1} i.m., and the skin over the basilic vein in the antecubital fossa was covered with local anaesthetic cream (prilocaine–lignocaine cream, EMLA). One hour later, a venous catheter was inserted on the dorsum of the hand and glycopyrrolate 3 μg kg^{-1} was injected i.v. A 70-cm

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TABLE I. *Demographic data (mean values (SD))*

	Control group	Alfentanil group
No. patients	10	10
Sex (M/F)	3/7	3/7
Age (yr)	44 (9)	40 (12)
Weight (kg)	65 (11)	71 (11)

catheter was inserted via the basilic vein on the contralateral arm pretreated with EMLA. The position of the catheter tip was shown to be in the right atrium or ventricle, either by the pressure wave form or by postoperative chest x-ray. An automatic sphygmomanometer (BP-103N Mark III, Nippon Colin Ltd, Tokyo, Japan) was used on the catheterized arm for monitoring of arterial pressure.

The ECG–aVR lead was displayed on an oscilloscope and recorded continuously. The QT intervals were retrospectively measured manually from the onset of the QRS-complex to the end of the T-wave. The mean QT interval of four successive beats was calculated. A heart rate correction ($QT_{corr.}$) was made according to the formula:

$$QT_{corr.} = \frac{QT}{\sqrt{R\text{–}R'}}$$

where the R–R interval is expressed in seconds [14].

The patients were allocated randomly to receive either alfentanil ($n = 10$) or saline ($n = 10$). When the monitoring equipment had been attached, the patient was allowed to rest for 20 min. Cardiovascular recordings were made and the first blood samples obtained. A coded 20-ml syringe containing either alfentanil 75 $\mu g\ kg^{-1}$ in saline or, in the control group, saline only, was injected as a rapid bolus via the peripheral cannula. One minute later, a sleep dose of thiopentone 3–7 $mg\ kg^{-1}$ was injected at a rate of 5 $mg\ s^{-1}$ to obtund the eyelash reflex, followed by suxamethonium 1 $mg\ kg^{-1}$. The patient's lungs were ventilated with 100% oxygen for 1 min with the end-tidal carbon dioxide concentration maintained at 5% throughout the study (Datex, Normocap). Laryngoscopy which lasted 10 s was performed with a MacIntosh laryngoscope and the trachea was intubated. Ventilation of the lungs with 100% oxygen continued for 5 min after tracheal intubation. If needed, supplementary doses of thiopentone 50 mg were added to treat inadequate depth of anaesthesia as indicated by signs such as lachrymation. All patients were anaesthetized by the same anaesthetist (L.L.). The code was not broken until the study was completed.

Blood from the right ventricle of the heart was sampled simultaneously with recording of the QT interval of the ECG and heart rate and the sphygmomanometer was restarted for recording arterial pressures at the following times:

1 = after 20 min rest, before induction of anaesthesia.
2 = after the administration of a sleep dose of thiopentone.
3 = 45 s after the end of injection of suxamethonium.
4 = after 10 s of laryngoscopy.
5 = 10 s after tracheal intubation.
6 = 5 min after intubation.

The blood samples were collected into prechilled polypropylene tubes containing EDTA, and immediately placed on ice. The blood was centrifuged at 0 °C, and the plasma stored in polypropylene tubes at −70 °C until required for analysis.

Plasma concentrations of catecholamines and the catecholamine metabolite 3,4-dihydroxyphenylglycol (DHPG) were measured using HPLC with electrochemical detection [15]. Slight reduction of the mobile phase methanol content allowed the concomitant separation and quantitation of DHPG, together with the amines. The method in its present form has intra-assay coefficients of variation of approximately 2% for noradrenaline, 4% for DHPG and 10% for adrenaline in the physiological concentration ranges.

Statistical analysis was performed using analysis of variance (ANOVA) for repeated measurements, with one between-factor (drug) and one within-factor (time), computed with BMDP2V and BMDP4V programs (BMDP Statistical Software Inc., U.S.A.). When pooled orthogonal components showed non-sphericity, Greenhouse–Geisser probability values were used and further tests, if required, were carried out with contrasts using separate error terms [16]. In other instances, traditional probability values and contrasts with a common error term were applied [17]. Student's paired and unpaired *t*-tests and the Chi-square-test were used, as appropriate.

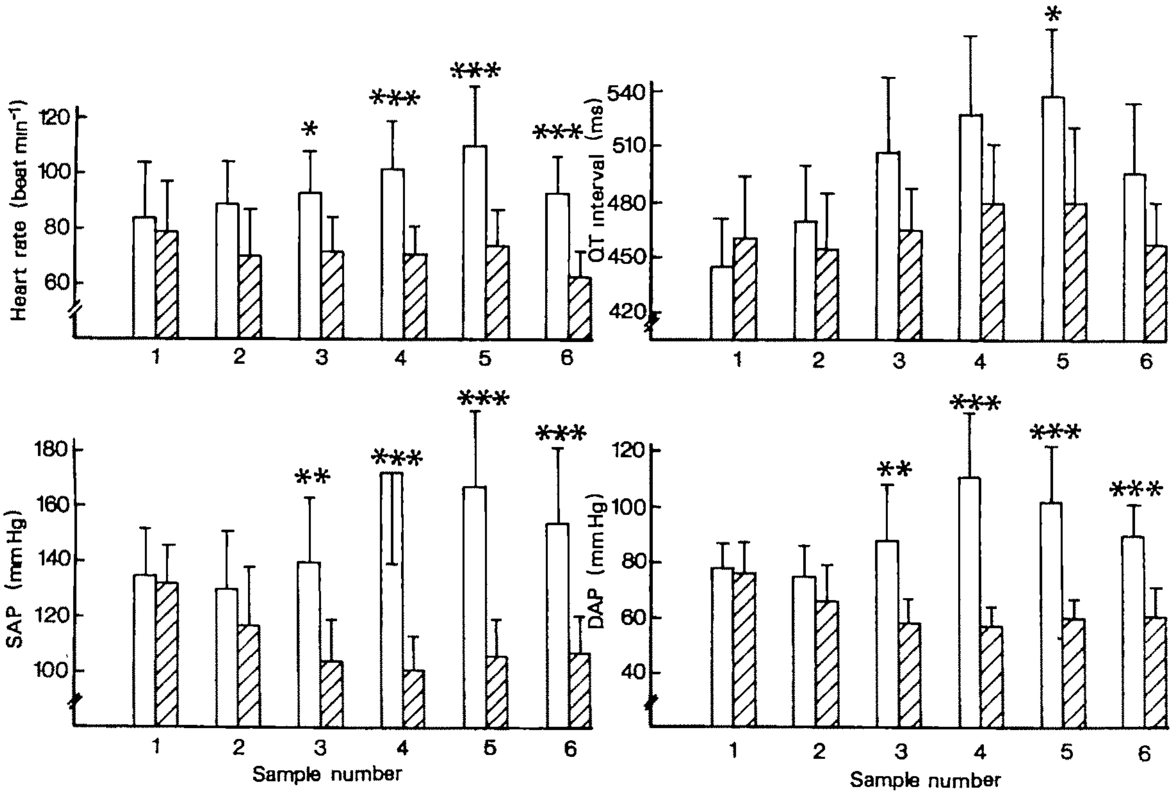

FIG. 1. Cardiovascular responses during induction of anaesthesia. Mean value (SD). □ = Control group; ▨-alfentanil group. 1 = Before anaesthetic; 2 = after thiopentone and alfentanil or saline; 3 = 45 s after injection of suxamethonium; 4 = after 10 s of laryngoscopy; 5 = 10 s after intubation; 6 = 5 min after intubation. $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ between groups (Bonferroni corrected P values).

RESULTS

The average sleep dose of thiopentone was 6.5 (SEM 0.3) mg kg^{-1} in the control group, and 4.1 (0.3) mg kg^{-1} in the alfentanil group ($P < 0.001$, *t* test). In the control group, eight of 10 patients received additional doses of thiopentone (50–150 mg) during the 5-min period after tracheal intubation, while none of the patients in the alfentanil group required more thiopentone. Chest wall rigidity occurred in four patients in the alfentanil group.

In the control group there was a significant prolongation of the QT interval after injection of suxamethonium and an increase in arterial pressure and heart rate. Laryngoscopy and intubation were associated with further increases in heart rate (31 % average increase from baseline), systolic and diastolic arterial pressure (21 % and 42 % increases), and the QT interval of the ECG (21 % increase) (fig. 1; see tables II and III for statistical evaluation). Four of these patients had significant cardiac arrhythmia; at laryngoscopy, ventricular ectopic beats were seen in two patients and multiple ectopics in bigeminy in one patient. A 33-yr-old woman developed ventricular ectopic beats followed by ventricular tachycardia after suxamethonium. The cardiac arrhythmias subsided spontaneously. The pre-anaesthetic mean QT interval for all patients was 450 (9) ms and 440 (5) ms (ns) in those who later developed arrhythmia. The QT interval increased to 537 (18) ms during the period of arrhythmia.

Cardiovascular responses to suxamethonium, laryngoscopy and intubation were abolished almost totally in the patients receiving alfentanil as pretreatment (fig. 1, tables II, III). Injection of alfentanil and a sleep dose of thiopentone was followed by decreases in heart rate (11 %) and

TABLE II. *Analysis of variance with one between- and one within-factor: effects of drug (alfentanil/saline) and time. Because of unequal variances, the following transformations were used: logarithmic (adrenaline), square-root (noradrenaline), reciprocal (arterial pressure)*

		Factor 1: drug	Factor 2: time	Interaction: drug × time
Heart rate	F	16.38	6.97	7.53
	P	0.0008	0.0026	0.0017
Systolic arterial pressure	F	31.31	3.58	18.42
	P	< 0.0001	0.030	< 0.0001
Diastolic arterial pressure	F	38.42	3.98	22.41
	P	< 0.0001	0.013	< 0.0001
QT-interval	F	6.33	22.46	8.27
	P	0.022	< 0.0001	< 0.0001
Noradrenaline	F	18.24	6.24	8.30
	P	0.0005	0.0016	0.0002
Adrenaline	F	7.57	24.28	1.26
	P	0.013	< 0.0001	0.30
DHPG	F	1.23	8.15	2.85
	P	0.28	0.0002	0.048

arterial pressure (maximal average decrease of 23% in systolic and 25% in diastolic pressures). The QT interval increased only minimally in the alfentanil group and no ECG abnormalities were observed ($P < 0.02$ compared with control, Chi-square test).

The mean concentration of noradrenaline in mixed venous plasma decreased similarly in both groups after thiopentone. In the control group the average concentrations of noradrenaline increased by 35% after suxamethonium, by a further 46% after laryngoscopy and further still, by 25%, after tracheal intubation (145% total increase) (fig. 2, tables II and III). Plasma concentrations of noradrenaline decreased slightly in the alfentanil group.

The mean preoperative concentration of noradrenaline in patients with cardiac arrhythmia during anaesthetic induction was 0.8 (0.2) nmol litre^{-1} and this increased to 1.6 (0.2) nmol litre^{-1}

TABLE III. *Significance levels* (P *values*) *from pairwise statistical tests of differences between the groups at the various time points, and for the different time points* v. *baseline within the groups* (*Bonferroni-corrected* P *values*). *ns = Not significant* (P ⩾ *0.05*). *NA = Noradrenaline; HR = heart rate; SAP, DAP = systolic, diastolic arterial pressures;* QT_{corr} *= heart rate correction*

Sample	NA	DHPG	HR	SAP	DAP	QT_{corr}
Control *v.* alfentanil						
1	ns	ns	ns	ns	ns	ns
2	ns	ns	ns	ns	ns	ns
3	< 0.05	ns	< 0.05	< 0.01	< 0.01	ns
4	< 0.001	ns	< 0.001	< 0.001	< 0.001	ns
5	< 0.001	ns	< 0.001	< 0.001	< 0.001	< 0.05
6	< 0.01	ns	< 0.001	< 0.001	< 0.001	ns
Control group						
1 *v.* 2	ns	ns	ns	ns	ns	ns
1 *v.* 3	ns	ns	ns	ns	ns	< 0.001
1 *v.* 4	ns	< 0.001	< 0.05	< 0.001	< 0.001	< 0.001
1 *v.* 5	< 0.05	< 0.001	< 0.01	< 0.001	< 0.001	< 0.001
1 *v.* 6	ns	< 0.05	ns	< 0.05	< 0.01	< 0.001
Alfentanil group						
1 *v.* 2	ns	ns	< 0.05	< 0.01	< 0.01	ns
1 *v.* 3	ns	ns	ns	< 0.001	< 0.001	ns
1 *v.* 4	ns	ns	ns	< 0.001	< 0.001	ns
1 *v.* 5	ns	ns	ns	< 0.001	< 0.001	ns
1 *v.* 6	ns	ns	< 0.05	< 0.001	< 0.001	ns

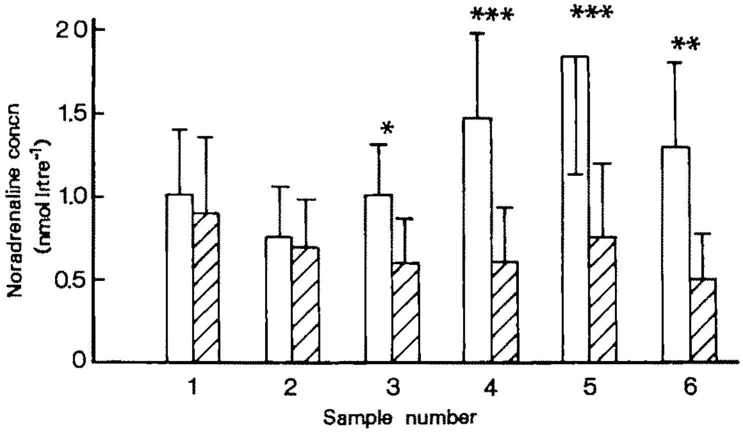

FIG. 2. Concentrations of noradrenaline in plasma from right heart ventricle during anaesthetic induction. Symbols as in figure 1. (For statistics, see tables II and III.)

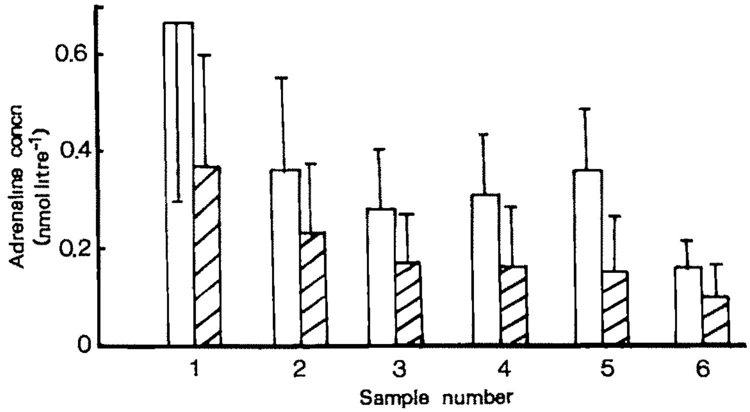

FIG. 3. Concentrations of adrenaline in plasma from right heart ventricle during anaesthetic induction. Symbols as in figure 1. (For statistics see table II.)

during arrhythmia. In all patients the mean preanaesthetic noradrenaline value was 0.95 (0.1) nmol litre^{-1}. The plasma concentrations of noradrenaline were significantly higher in the control group after administration of suxamethonium and thereafter, when compared with the alfentanil group (fig. 2).

The plasma concentration of adrenaline at baseline was greater in the control group than in the group receiving alfentanil, but both groups showed a similar, decreasing trend throughout the study (fig. 3). DHPG in plasma increased significantly (by 25%, on average) in the control group during the procedure, and was unaltered in the alfentanil group (tables II–IV). The changes in the QT interval were directly proportional to the changes in plasma noradrenaline concentrations in the control group during induction (fig. 4). Linear regression analysis gave the equation $y = 52x + 7$ with $r = 0.67$ ($P < 0.001$).

TABLE IV. *Mean (SD) concentrations (nmol litre^{-1}) of DHPG in plasma from right heart ventricle during induction of anaesthesia*

	Sample number					
	1	2	3	4	5	6
Control group	4.91 (0.74)	4.59 (0.93)	5.30 (0.94)	5.63 (0.74)	5.73 (0.89)	5.41 (0.90)
Alfentanil group	4.79 (0.60)	4.80 (0.56)	4.91 (0.88)	5.01 (0.77)	5.13 (0.83)	4.86 0.69)

DISCUSSION

We have found that pretreatment with alfentanil totally obtunded the cardiovascular and catecholamine responses to tracheal intubation in healthy patients. In the control group receiving saline, plasma concentrations of noradrenaline and its metabolite, DHPG, increased after administration of suxamethonium and increased further at laryngoscopy and intubation. Changes in the QT interval on the ECG correlated directly with the changes in plasma concentrations of noradrenaline.

Increases in arterial pressure and heart rate observed in the control group in our study were similar to those reported in numerous earlier studies with patients not receiving an opioid as part of the anaesthetic medication [4, 5, 8, 18]. The incidence of cardiac arrhythmia in association with laryngoscopy was of the same order as that observed elsewhere in healthy patients [10, 19]. Our data are also consistent with the results obtained by Prys-Roberts and others [5] and by Shribman and others [7].

There is evidence that suxamethonium stimulates cardiac sympathetic ganglia [20, 21]. Increases in arterial pressure and heart rate after suxamethonium have been demonstrated previously in normotensive patients [18]. In our control group, the plasma concentrations of noradrenaline and DHPG, and heart rate and arterial pressures tended to increase after administration of suxamethonium. Nigrovic and others [22] found a significant increase in arterial plasma concentration of noradrenaline after suxamethonium. This increase may have been overestimated, as they also used halothane, which decreases the pulmonary uptake of noradrenaline [23] and may also liberate noradrenaline from sympathetic nerves [24]. Catecholamines, especially noradrenaline, are taken up selectively by the lungs to a significant extent [25, 26]. Therefore, we sampled venous blood from the right ventricle of the heart for determination of plasma catecholamine concentrations. Thus even small increases in plasma concentrations of noradrenaline could be detected in the present study as was found also by Derbyshire and others [4], who observed higher concentrations of catecholamines in central venous than in arterial or peripheral venous blood.

Plasma DHPG was measured as an indicator of intraneuronal metabolism of noradrenaline [27], and it followed a temporal pattern similar to that of changes in plasma noradrenaline. Thus in-

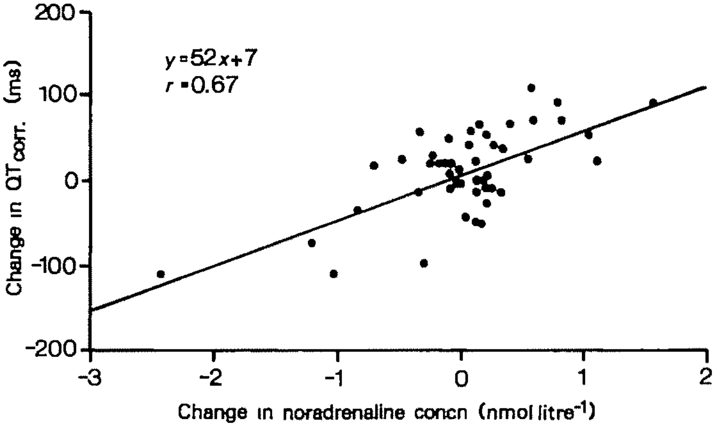

FIG. 4. Relationship between changes in mixed venous plasma noradrenaline concentrations and in the heart rate-correlated QT interval on the ECG in patients not receiving alfentanil during anaesthetic induction. Regression line for 48 points: $y = 52x+7$; $r = 0.67$ ($P < 0.001$).

creases in plasma DHPG appear to reflect augmented release of noradrenaline from sympathetic nerves. The greater increase in diastolic than in systolic arterial pressure in this study also indicates the predominance of noradrenaline with a pronounced α-mimetic activity. Pretreatment with alfentanil inhibited these cardiovascular and noradrenaline responses related to suxamethonium.

In the present study, the concentration of adrenaline in plasma decreased during induction of anaesthesia, as was documented by Russell and others [3]. In their study, patients were premedicated with morphine and atropine, and in the present study we used diazepam combined with pethidine and glycopyrrolate. Increased concentrations of adrenaline after tracheal intubation have been demonstrated in normotensive [4, 6–8] and hypertensive [5] patients. However, in all the studies showing increases of adrenaline the patients were premedicated without an opioid. Thus it may be suggested that premedication with an opioid, even in low doses, prevents the increase of adrenaline, but not that of plasma noradrenaline, after laryngoscopy and intubation.

In a group of patients, 50 % of whom received β-adrenoceptor blockers or other antihypertensive therapy, alfentanil in doses of 10 μg kg^{-1} or 40 μg kg^{-1} was shown to obtund cardiovascular responses to intubation [8], but alfentanil 40 μg kg^{-1} was associated with profound hypotension and bradycardia. In healthy patients, alfentanil 10 μg kg^{-1} was not sufficient to obviate the cardiovascular response to intubation [28]. In contrast, doses of alfentanil 100–250 μg kg^{-1} produced no hypotension or bradycardia in unpremedicated young adults [13]. In the present study, alfentanil 75 μg kg^{-1} and a sleep dose of thiopentone produced a significant although not clinically important decrease in arterial pressure. The hypotension and bradycardia observed after alfentanil [8] may have been a result of the lack of anticholinergic premedication.

Suxamethonium was used in the present study and also in that by McDonnel and others [13]. The lack of hypotension and bradycardia after alfentanil in our study was possibly related to the use of suxamethonium, which has a sympathomimetic activity, as demonstrated in the present study. Our patients also received an anticholinergic, which protected against bradycardia.

We wanted to use a relatively high dose of alfentanil in order to prevent the cardiovascular response to laryngoscopy. Fentanyl 6 μg kg^{-1} blunts this response [11]; the analgesic potency ratio between fentanyl and alfentanil has been stated as 1:3 [29], but also 1:13 [30]. Four of 10 of our patients treated with alfentanil 75 μg kg^{-1} developed chest wall rigidity, which made ventilation of the lungs difficult during induction of anaesthesia. A smaller dose of alfentanil (30 μg kg^{-1}) may be ideal to prevent the sympathoadrenal response to tracheal intubation as reported by Black and others [31].

In our control group, the QT interval was prolonged significantly after the administration of suxamethonium and further after laryngoscopy and intubation, thereby confirming earlier reports [10, 19, 32, 33]. The changes in QT interval correlated directly with the changes in plasma concentration of noradrenaline. There is evidence that the QT interval is prolonged in the presence of high plasma concentrations of catecholamines and that this prolongation is a predictor of cardiac arrhythmia [32]. The QT interval was prolonged during serious ventricular arrhythmia after myocardial infarction [34, 35] and increased concentrations of catecholamines have been observed in patients with myocardial infarction during arrhythmia immediately before cardiac arrest [36]. To our knowledge, there have been no studies in which prolongation of the QT interval and catecholamine concentrations in plasma have been measured simultaneously. The present data show that, in healthy persons, the prolongation of the QT interval closely reflects the increase in plasma concentrations of noradrenaline.

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EFFECT OF PROLONGED SEDATION WITH PROPOFOL ON SERUM TRIGLYCERIDE AND CHOLESTEROL CONCENTRATIONS

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AND J. M. HACKL

SUMMARY

We compared changes in serum lipid concentrations in ICU patients receiving a 3-day continuous infusion of propofol with those in patients receiving conventional sedation. No adverse effects were observed and the serum lipid concentrations were not significantly influenced by propofol. It is concluded that propofol might be a suitable agent for long-term sedation in the ICU, although serum lipid concentrations should be monitored throughout its administration.

The short duration of action and minor cardiovascular and endocrinological side effects [1] of propofol (di-isopropyl-phenol) seem to render this drug suitable for prolonged sedation of patients undergoing mechanical ventilation in the Intensive Care Unit (ICU). Propofol is formulated as a 10% oil in water emulsion [2] and some effects of long term administration of propofol on serum lipid concentrations might be expected. Although propofol has been used for sedation in the ICU [3], to our knowledge its effects on serum lipid have not been studied.

This study was designed to investigate primarily any alterations in the normal serum triglyceride, cholesterol and HDL-cholesterol concentrations which might occur during a 3-day continuous infusion of propofol in ICU patients receiving parenteral nutrition.

PATIENTS AND METHODS

The study was approved by the local Medical Ethics Committee. We studied 20 non-septic ICU patients. None had a medical history of anomalies in lipid metabolism, or diseases of the pancreas or gastrointestinal system. Types of injury, severity of illness [4] and injury score [5] are shown in table I.

The patients were allocated randomly to two groups. In group 1 sedation was induced with propofol 2 mg/kg body weight initially, followed by a continuous i.v. infusion of 0.2 mg kg^{-1} h^{-1} and additional bolus doses of 1 mg kg^{-1}, if needed, before nursing manoeuvres. Infusion rates were adjusted to provide sufficient sedation to keep patients comfortable and prevent anxiety. In group 2, sedation was achieved with pentobarbitone 2 mg kg^{-1} and diazepam 0.3 mg kg^{-1} (both up to six times within 24 h) adjusted to clinical needs.

Patients in both groups received comparable amounts of pancuronium for relaxation (0.1

TABLE I. *Details of patients studied (mean (SD))*

	Group 1 (propofol)	Group 2 (Intralipid)
n	10	10
Age (yr)	46 (6)	46 (6)
Weight (kg)	71 (2)	68 (3)
Sex (M/F)	5/5	6/4
Diagnosis		
Multiple trauma	4	5
Blunt brain trauma	6	5
APACHE II score	28 (2)	25 (2)
ISS Score	32 (4)	32 (2)

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TABLE II. *Composition of 100 ml of administered i.v. lipids*

	Soya bean oil	Lecithin	Glycerol	Di-isopropylphenol
Propofol	10 g	1.2 g	2.5 g	10 mg
Intralipid	20 g	1.2 g	2 25 g	—

TABLE III. *Experimental procedure*

	Pretreatment period	Period of treatment Day 1	Day 2	Day 3
Group 1	—	Propofol	Propofol	Propofol
Group 2	—	Intralipid	Intralipid	Intralipid
Measurements of serum lipid concns (both groups)	+	+	+	+

mg kg^{-1} i.v. up to 12 times within 24 h) when required to facilitate mechanical ventilation, and piritramide (0.1–0.2 mg kg^{-1} up to six times within 24 h) to provide analgesia. The lungs were ventilated mechanically to achieve normocapnia with oxygen-enriched air. Ventilation was adjusted step by step following a regimen used routinely in our ICU [6].

All patients received parenteral nutrition via a central venous line and an enteral diet used routinely through a feeding tube (Peptisorb). Caloric input was up to 25 kcal kg^{-1} day^{-1}, as required by each patient. Nutrition was increased stepwise and we aimed to administer up to 6 g kg^{-1} of carbohydrate, 1.5 g kg^{-1} of protein and 1 g kg^{-1} of lipids per day. Patients in group 2 received 20% Intralipid 100 ml per day by continuous infusion. Patients in group 1 received no parenteral lipids apart from that contained in their propofol infusion. The individual compositions of the lipids administered are shown in table II.

Blood samples were taken according to a predetermined schedule (table III), and serum triglyceride, cholesterol and high-density-lipoprotein (HDL)-cholesterol concentrations were measured before and during the 3-day period of treatment. Chemical analyses of the samples were performed by standard laboratory methods using an enzymatic determination with glucose peroxidase for triglycerides and cholesterol [7] and a precipitating procedure with polyethyleneglycol and phosphate buffer for HDL-cholesterol [8].

The desired sedation was achieved when patients remained calm as observed by the investigators and by the nursing staff, who had also been instructed to observe for adverse effects such as allergic reactions or other unusual effects during the 3-day period of treatment.

For statistical analysis, analysis of variance for paired data was used for within-group comparisons. Student's *t* test for unpaired data was used to compare observations between groups. Differences were considered to be significant at $P < 0.05$.

TABLE IV. *Mean (SD) daily caloric supply (kcal)*

	Group 1 (propofol)	Group 2 (Intralipid)
Pretreatment period	998 (243)	1161 (140)
Period of treatment		
Day 1	1470 (168)	1677 (210)
Day 2	1802 (196)	1652 (198)
Day 3	1918 (196)	1776 (211)

TABLE V. *Mean (SD) parenteral lipid administration (g day^{-1})*

	Group 1 (propofol)	Group 2 (Intralipid)
Day 1	34.45 (25.6)	20 (0)
Day 2	39.35 (23.0)	20 (0)
Day 3	36 02 (21.7)	20 (0)

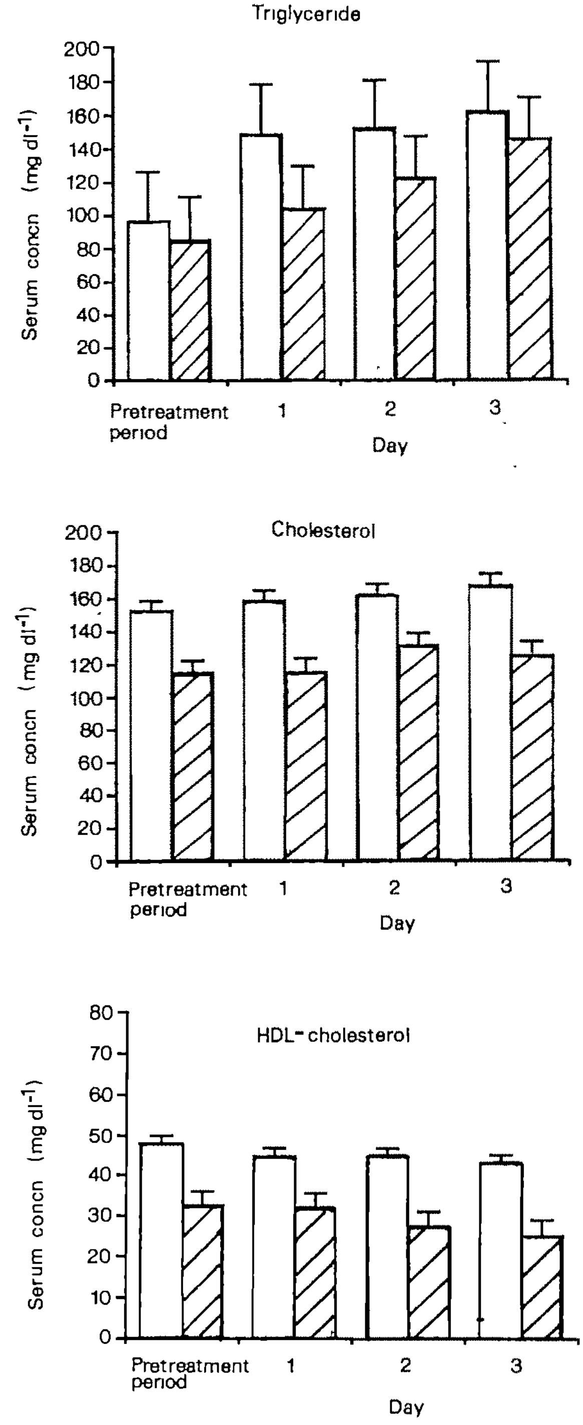

FIG 1 Mean and SD serum concentrations of triglyceride, cholesterol and HDL-cholesterol (mg dl^{-1}) during the period of pretreatment and the 3-day period of treatment (days 1, 2 and 3) in patients receiving propofol (□) or conventional sedation (▨).

RESULTS

The two groups did not differ in age, weight or sex distribution (table I).

Daily caloric input was similar in both groups (table IV). The total amount of parenteral lipids administered for nutrition (table V) and the mean serum lipid concentrations (fig. 1) were greater in group 1 but, compared with the pretreatment-period, the changes in triglyceride, cholesterol or HDL-cholesterol concentrations were not significant during the 3 days of fat administration (fig. 1) and they never exceeded laboratory norms (triglycerides 40–160 mg dl^{-1}, cholesterol 120–220 mg dl^{-1}, HDL-cholesterol 35–68 mg dl^{-1}) [9].

In one patient, serum concentrations of trigylceride exceeding 500 mg dl^{-1} necessitated termination of the propofol infusion after the first day of administration. This patient had inadvertently received 20 % Intralipid 100 ml at the same time, and consequently was excluded from the study and replaced by another patient. During treatment, the dose of propofol required for optimal sedation varied widely within and between individual patients, but could always be achieved by adjusting the rate of infusion. This resulted in a considerable increase in total propofol consumption in all patients. The mean total dose of propofol used was approximately 2 mg kg^{-1} h^{-1} (infusion plus additional bolus doses before nursing manoeuvres). No allergic side effects were noted in any patient.

DISCUSSION

In animal models, propofol has been reported to produce burst suppression patterns similar to those of barbiturates [10]. The pharmacological effects of this compound are of short duration, resulting in rapid awakening. These properties render propofol a suitable sedating agent.

Because of the pharmaceutical composition of the carrier substance, problems may arise during long term administration of propofol. Fat emulsions should be administered only to patients who are devoid of inborn or acquired anomalies of lipid metabolism and enzyme systems. Our data indicate that significant changes in concentrations of triglyceride should not occur, provided that the pre-treatment values fall within the normal range. The greater mean values observed in patients receiving propofol correspond with the larger amounts of lipid solvent administered, but these differences were not significant. However, changes in post traumatic metabolism may also have caused disturbances of the enzyme systems responsible for serum lipid clearance and metabolism [11].

Interestingly, HDL-cholesterol concentrations also tended to be greater in patients receiving propofol. We cannot explain these findings, but the possible protective properties of HDL-cholesterol [12] may render this a desirable side effect of propofol infusion.

In summary, infusion of propofol produced adequate sedation in adult patients who required mechanical ventilation in the ICU. When used for long term sedation by continuous infusion, the lipid solvent for propofol may replace separate infusion of parenteral lipids for nutrition. The contraindications to long term infusion of propofol include inborn and acquired anomalies of lipid metabolism [13] and known allergy to this agent. Daily monitoring of serum concentrations of lipids is necessary, especially if high doses are administered for long periods. However, further studies are required to confirm the safety and efficacy of propofol in a greater number and variety of ICU patients.

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INFLUENCE OF PREOPERATIVE GASTRIC ASPIRATION ON THE VOLUME AND pH OF GASTRIC CONTENTS IN OBSTETRIC PATIENTS UNDERGOING CAESAREAN SECTION

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SUMMARY

Aspiration of gastric contents, the most common anaesthetic cause of maternal mortality, is decreased by emptying of the stomach and the use of antacids and H_2-receptor antagonists. One hundred and eighty-three mothers presenting for emergency Caesaren section were allocated to three groups. In group 1, the stomach was emptied before operation via an orogastric tube and thereafter 30 ml of sodium citrate 0.3 mol litre^{-1} was ingested 5–15 min before induction of general anaesthesia (our usual practice). Group 2 received only 30 ml of sodium citrate 0.3 mol litre^{-1}. Group 3 received ranitidine 50 mg i.v. before operation, 5–15 min before induction of anaesthesia, in addition to sodium citrate Our results show that preoperative gastric emptying with an orogastric tube followed by sodium citrate is preferred if anaesthesia should be induced 15–20 min later. However, the use of ranitidine and sodium citrate is preferred at subsequent times. Although our data show that preoperative gastric emptying decreased the mean intragastric volumes before Caesarean section, the number of patients at risk of acid aspiration was not reduced. In view of these findings and the unpleasantness of orogastric intubation, we suggest that routine preoperative gastric aspiration via an orogastric tube is not justified, although the manoeuvre should still be used following a recent meal.

Pulmonary aspiration of gastric contents continues to be of major concern in obstetric anaesthesia [1]. The combination of an intragastric pH of 2.5 or less with a gastric contents volume greater than 25 ml are generally regarded as placing the patient at risk of chemical aspiration pneumonitis [2], although this condition has been reported in a patient following the aspiration of stomach contents of pH 3.5 [3], and intragastric pH values of greater than 2.5 may cause pulmonary damage in rats [4].

Attempts to increase the pH of gastric contents have met with varying degrees of success [5,6]. The use of antacids either alone [7] or in combination with H_2-receptor antagonists [8] increases pH adequately in the majority of patients, but this is less effective in patients presenting in labour for emergency Caesarean section [9].

Several methods have been used to decrease intragastric volumes before emergency Caesarean section, including preoperative orogastric intubation [5,10], mechanical stimulation of vomiting [11], i.v. apomorphine [12] and metoclopramide [13,14]. For many years, at King Edward VIII Hospital it has been routine practice to aspirate the stomach via a wide bore (28-French gauge) stomach tube before administration of 30 ml of sodium citrate 0.3 mol litre^{-1} in patients presenting for emergency Caesarean section. Exceptions to this practice are patients with hyper-

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tension, cardiac disease, fetal distress or acute haemorrage.

The unpleasant nature of orogastric intubation has led many of our anaesthetists and surgical colleagues to question its value. However, before instituting a major change in labour ward policy, we decided to investigate the effect of preoperative gastric emptying on the intragastric pH and volume of stomach contents at induction of anaesthesia. We have compared three treatment groups: preoperative gastric emptying followed by oral sodium citrate, preoperative oral sodium citrate alone, and preoperative oral sodium citrate in combination with a single i.v. injection of ranitidine.

PATIENTS AND METHODS

We studied 183 healthy mothers (aged 18–38 yr) referred for emergency Caesarean section at 36–42 weeks gestation. Patients with evidence of cardiopulmonary disease, hypertension, diabetes or gross obesity (> 110 kg) were excluded. Informed consent was obtained and the study was approved by the Ethics and Standards Committee of this Medical Faculty.

Gastric emptying was performed using an orogastric tube before operation in 63 patients and the tube was removed before induction of anaesthesia. Thereafter 30 ml of sodium citrate 0.3 mol $litre^{-1}$ was administered by mouth and the time noted (group 1). Another 60 patients (group 2) received sodium citrate only, while group 3 (60 patients) received ranitidine 50 mg by slow (1 min) i.v. injection 5 min before induction of anaesthesia, in addition to oral sodium citrate.

A standard general anaesthetic technique was used with the usual precautions against aortocaval occlusion. All patients received metoclopramide 10 mg i.v. followed by glycopyrrolate 0.2–0.4 mg i.v. or atropine 0.3–0.6 mg i.v. [15]. After preoxygenation, anaesthesia was induced with thiopentone 3–4 mg kg^{-1}. Cricoid pressure was applied with induction and relieved following intubation of the trachea with a cuffed tracheal tube; this was facilitated by suxamethonium 1–1.5 mg kg^{-1} i.v. Anaesthesia was maintained with 0.5 % halothane or 1% enflurane and 50% nitrous oxide in oxygen, and the lungs ventilated mechanically to achieve normocapnia. Further neuromuscular blockade was obtained using alcuronium 12.5 mg and increments of 2.5 mg when necessary.

A 16-French gauge nasogastric tube was inserted after tracheal intubation and its position verified by the simultaneous injection of air and auscultation over the epigastrium. Each group of patients was classified further into six subgroups, A–F. Aspiration of gastric contents for pH and volume measurement was performed at 15–20 min in group A, at 1 h in group B, 2 h in group C, 2.5 h in group D, 3 h in group E and at 3.5 h in group F. Patients were allocated randomly to groups 1 and 2, while group 3 was studied after the completion of groups 1 and 2 because of initial unavailability of ranitidine for i.v. use. Although the technique of gastric aspiration cannot guarantee complete gastric emptying, and volumes recorded reflect only the maximum gastric aspirate obtained at the time, every effort was made to increase yield by manipulation of the tube.

At delivery, syntocinon 5 units was given i.v. and 15 units was added to the i.v. infusion. At termination of surgery, the residual effects of alcuronium were antagonized by injection of glycopyrrolate 0.8 mg with neostigmine 2.5–5 mg i.v. Gastric contents were sampled at the times noted above, measured volume was recorded and the pH measured with Merck indicator paper; the results were standardized against a Beckman instrument pH electrode. A good correlation between the results obtained with the Merck paper and the various pH electrodes has been reported previously [5, 16].

Volume and pH data were compared using the Mann–Whitney *U* test. The numbers of patients considered to be at risk of pulmonary aspiration in each group were compared using the Fisher Exact Test. For the purposes of this study our definition of an "at risk" patient was one with an intragastric volume > 25 ml and pH $\leqslant 3.5$. $P < 0.05$ was considered to be statistically significant.

RESULTS

In all groups the colour of the gastric content ranged from clear to deep green. The latter suggested the presence of bile, but this was not always associated with an alkaline pH. In three patients, no gastric contents was aspirated. All three had had a stomach tube passed before operation and gastric aspiration performed 15–20 min after ingestion of sodium citrate. All patients were in active labour for an indeterminate period of time before admission. The majority received a combination of pethidine 100 mg and

TABLE I. *Mean (SD) weight, age, gestation and parity in each group. No significant difference between groups*

	Group 1 ($n = 68$)	Group 2 ($n = 60$)	Group 3 ($n = 60$)
Weight (kg)	71.7 (6.7)	79.1 (24.4)	68.2 (6.8)
Age (yr)	26.9 (5.1)	23.7 (4.2)	24.4 (4.7)
Gestation (weeks)	39.1 (0.7)	38.4 (1.5)	38.6 (1.0)
Parity	2.5 (0.7)	1.8 (1.2)	1.3 (1.2)

TABLE II. *Mean (SD) intragastric pH in each group at the various times of aspiration. Significant differences ($P < 0.02$): *compared with groups 2 and 3 at 15–20 min; †compared with groups 1 and 2 at 2, 2.5 and 3 h; §compared with group 1 at 3.5 h*

Time	Group 1 ($n = 10$)	Group 2 ($n = 10$)	Group 3 ($n = 10$)
15–20 min	6.0 (0.8)*	4.9 (1.0)	5.0 (1.0)
1 h	4.8 (0.7)	5.0 (1.0)	5.5 (0.9)
2 h	4.5 (0.8)	4.7 (0.7)	5.6 (0.8)†
2.5 h	4.7 (0.3)	4.6 (1.1)	6.1 (0.7)†
3 h	4.7 (0.5)	5.0 (0.8)	5.4 (0.6)†
3.5 h	4.0 (0.9)	4.4 (0.9)	5.1 (0.6)§

TABLE III. *Mean (SD) intragastric volumes in each group at the various times of aspiration. *Significantly different ($P < 0.05$) from groups 2 and 3 at that time. No significant difference in volumes between groups 2 and 3 at any time*

	Group 1 ($n = 13$)	Group 2 ($n = 10$)	Group 3 ($n = 10$)
15–20 min	9.9 (7.3)*	43.5 (33.5)	38.6 (29.0)
1 h	30.7 (14.1)*	65 (32.0)	57.4 (29.4)
2 h	24.1 (14.9)*	68.7 (70.0)	54.7 (31.6)
2.5 h	34.8 (13.7)*	57 (21.2)	53.3 (19.1)
3 h	52 (25.2)	51.7 (26.1)	44.1 (23.8)
3.5 h	73.2 (94.9)	65.8 (24.8)	52.9 (25.4)

TABLE IV. *Number of patients in each group with pH < 3.5*

	Group 1	Group 2	Group 3
15–20 min	0	1	1
1 h	1	1	0
2 h	1	1	0
2.5 h	0	1	0
3 h	0	0	0
3.5 h	1	1	0

promazine 50 mg i.m. for labour pains. The slow i.v. injection of ranitidine did not cause any adverse effects.

Maternal age, weight, gestation and parity were similar in the three groups (table I).

TABLE V *Number of patients in each group with gastric volume > 25 ml*

	Group 1	Group 2	Group 3
15–20 min	0	7	6
1 h	8	8	8
2 h	4	8	9
2.5 h	7	9	9
3 h	8	8	10
3.5 h	8	9	9

TABLE VI. *Number of patients "at risk"*

	Group 1	Group 2	Group 3
15–20 min	0	0	0
1 h	1	1	0
2 h	1	1	0
2.5 h	0	1	0
3 h	0	0	0
3.5 h	1	1	0

Mean pH was significantly greater in group 1 than in groups 2 and 3 ($P < 0.02$) at 15–20 min and was significantly greater in group 3 at 2, 2.5 and 3 h than in other two groups and significantly greater in group 3 than in group 1 at 3.5 h ($P < 0.02$) (table II).

Measured volumes were significantly lower ($P < 0.05$) in group 1 than in groups 2 and 3 at 15–20 min, 1, 2 and 2.5 h. There was no significant difference in volumes between group 2 and 3 at any time (table III). No patient was found to be at risk in any group at 15–20 min. Furthermore, there were no patients at risk in group 3 (i.v. ranitidine and sodium citrate) at any time, whereas there were three patients considered to be "at risk" in group 1, and four in group 2. However, there was no significant difference in the number of patients at risk in groups 1 and 2 ($P = 0.35$), groups 1 and 3 ($P = 0.13$) or groups 2 and 3 ($P = 0.06$) (tables IV–VI).

DISCUSSION

The results of our study appear to confirm previous reports [5,17–19]. Sodium citrate alone produced an intragastric pH < 3.5 for at least 15–20 min. However, one patient had an intragastric pH of 3.5 and the mean intragastric pH in this group was significantly lower than in those patients who also had their stomachs emptied before operation. This result is not surprising when the higher sample volumes are taken into account, indicating that decreasing intragastric volume before administration of an antacid is of value in increasing pH. This effect may not persist for longer than 15–20 min, despite significantly smaller volumes (presumably because of continued gastric acid secretion) and the period of emergence from anaesthesia may not be affected. However, in the patients who received i.v. ranitidine, pH values were significantly greater than in both the other groups after 2 h, but intragastric volumes were not significantly smaller. This suggests that ranitidine decreased hydrogen ion secretion, but not the total volume of secretion, in these patients. There is, however, some evidence to suggest that ranitidine does decrease gastric volume in elective Caesarean section [20]. It is possible that a larger dose of ranitidine, a longer period following administration, or both, might exert a beneficial effect on volume. Although there was no significant difference in mean pH values between the groups at 1 h, all the values in the patients given ranitidine exceeded 4, whereas each of the other groups at this time included a patient considered to be at risk from the combination of low pH and large gastric volume.

Mean measured volumes at 15–20 min, 1, 2 and 2.5 h after administration of sodium citrate were significantly smaller in patients who underwent gastric emptying before operation, although only at 15–20 min were there no patients with a measured volume greater than 25 ml. However, the evidence for a critical volume necessary to produce acid pneumonitis is somewhat tenuous. Unpublished work by Roberts and Adamsons, alluded to in Roberts and Shirley's paper of 1974 [2], suggested that, in Rhesus monkeys, aspiration of gastric contents in excess of 0.4 ml kg^{-1} (approximately 25 ml in human parturients) would be hazardous. Animal studies undertaken before this work involved the tracheal instillation of fluid up to 4 ml kg^{-1} of varying pH in order to produce the acid aspiration syndrome [11,21]. Recently, it has been shown [22] that human aspirate (pH 1, volume 0.4 ml kg^{-1}) instilled into monkeys did *not* produce the clinical signs of aspiration pneumonitis.

It is possible that we are being unrealistic in pursuing an ideal of less than 25 ml of stomach contents in patients for emergency Caesarean section. A wide bore orogastric tube would seem to be the best way to achieve this, but the technique cannot guarantee an intragastric volume of less than 25 ml (particularly after 1 h).

Although the use of a stomach tube to decrease intragastric volume before general anaesthesia is often recommended in the literature [9,10], we know of only one study that has examined the effects of this technique before emergency obstetric anaesthesia [23]. Of alternative techniques, induced vomiting, whether mechanical or pharmacological, is as unpleasant as the passage of an orogastric tube and i.v. metoclopramide may not be effective following the administration of opioid analgesics [24]. In a comparison between preoperative gastric aspiration by stomach tube and i.v. apomorphine, Holdsworth, Furness and Roulston [23] concluded that both methods were equally effective in decreasing volume, and that neither guaranteed an empty stomach.

Ranitidine i.v. produced higher mean pH values from 1 h onward but, not surprisingly, did not cover induction of anaesthesia. Sodium citrate alone is inadequate for emergency Caesarean section as the beneficial effect lasts only for 15–20 min and further doses of sodium citrate must be given to cover the emergence period. Oral ranitidine has been given to obstetric patients 2 h before surgery together with sodium citrate, producing a gastric pH > 3 [25]. Ranitidine has the added advantage that it increases lower oesophageal sphincter tone [26] and does not possess many of the side effects of cimetidine [25,27–31]. We observed no adverse clinical effects following slow i.v. injection of ranitidine in our 60 patients. The reason for giving ranitidine only 5 min and not the recommended 60 min before induction was that we wished to assess the extent and duration of any effects of ranitidine at fixed time intervals in comparison with the other two groups.

Our results show, not surprisingly, that preoperative gastric emptying significantly decreased mean intragastric volumes before Caesarean section, but that this did not significantly decrease the number of patients at risk of acid aspiration. At 15–20 min none of the groups had patients at risk, implying that sodium citrate alone might be effective for a short period, although far larger numbers would be needed in each group in order to exclude a type II error. Although it is possible to reduce intragastric volume by gastric aspiration before operation, the unpleasantness of the procedure, the uncertain role of volume in the pathogenesis of the acid aspiration syndrome, and the inability of the technique to reduce the number of at risk patients, does not justify its routine use. However, we shall continue to use orogastric aspiration following a recent meal. The use of i.v. ranitidine in addition to sodium citrate may be useful if given at least 1 h before operation, and this provides additional prophylaxis for the recovery period following general anaesthesia.

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BLOOD–BRAIN BARRIER TO PERTECHNETATE FOLLOWING DRUG-INDUCED HYPOTENSION

P. R. COOK, D. MYERS, M. BARKER AND J. G. JONES

SUMMARY

The integrity of the blood–brain barrier (BBB) was examined in rabbits, in terms of the partition of ^{99m}Tc-pertechnetate ($^{99m}TcO_4^-$) between brain and blood, following intracarotid injection of hypertonic arabinose, hypertension (168 mm Hg and 10% inspired carbon dioxide), or hypotension (< 20 mm Hg for 15 min). Corrections were made for changes in tissue blood contents, using chromium-51 as a red cell marker. In control animals the mean brain:blood ratio was 0.038 (range 0.027–0.052). Following arabinose there was a five-fold increase in mean BBB permeability (mean brain:blood ratio 0.192 (0.070–0.378)). There was no change after hypertension and carbon dioxide (mean ratio 0.034) or after hypotension (mean ratio 0.032), despite an increase in cerebral extracellular potassium. Examination of other tissues showed no change in the $^{99m}TcO_4^-$ tissue/blood partition in heart muscle in any study but, following hypotension, ratios in the kidney (mean ratio 1.63) and, to a lesser extent, the liver (mean ratio 1.37) had increased, suggesting an abnormality of active transport under these conditions. We conclude that, while $^{99m}TcO_4^-$ tissue/blood partitioning revealed osmotic disruption of the BBB, profound hypotension with evidence of brain cell damage did not change BBB permeability to the same marker. Hypotension may influence active transport of this ion in liver and kidney.

There is some disagreement on the effects of profound hypotension and ischaemia on the blood–brain barrier (BBB). In a study in the gerbil, of the penetration of the BBB by Evan's Blue–albumin following clamping of one carotid artery [1], it was found that no breakdown of the BBB occurred with less than 30 min occlusion, longer periods of ischaemia producing breakdown which occurred in some animals only at 5–29 h after restoration of blood flow. In contrast, dogs subjected to hypotension to a mean cerebral perfusion pressure of 30–45 mm Hg showed extensive breakdown of the barrier to Evan's Blue–albumin complex immediately after the end of the hypotensive episodes [2]. Differentiating between the effects of ischaemia and infarction, Petito and colleagues [3] concluded that the BBB remains impermeable to large molecules for 15–30 min after reperfusion following ischaemia without infarction. In the same model Sage, Van Uitert and Duffy [4] showed that, in contrast to large molecules, a small molecule (leucine) did leak through the BBB 15 min after reperfusion. Some of these differences may result from the dissimilar procedures used for producing ischaemia, or species differences, small molecules seeming more sensitive than large ones to breakdown of the BBB.

If breakdown of the BBB to large molecules is widespread following hypotension [2], it might be useful to develop a probe molecule technique for clinical use as a sensitive diagnostic and prognostic test of brain injury in unconscious man.

We chose the probe molecule ^{99m}Tc-pertechnetate ($^{99m}TcO_4^-$, mol. wt 163 Daltons) for two reasons: the radionucleotide has a short half-life, rapid elimination from the body, and is readily available and easily detected; and it has been shown [4] that a small molecule is even more sensitive to BBB breakdown than is albumin.

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Although there are a number of techniques used to detect brain injury *in vivo*, all are invasive and impractical for clinical use. The technique for measuring the change in extracellular potassium is well established and we have used this as an indicator of brain injury following hypotension. To evaluate the permeability model, we have compared the partitioning of $^{99m}TcO_4^-$ between blood and brain and other tissues, in control animals, and following osmotic disruption of the BBB, acute hypertension or profound hypotension.

MATERIALS AND METHODS

Thirteen New Zealand White rabbits (mean weight 3.9 kg (range 2.8–5.3)), were anaesthetized with Hypnorm (fluanisone 3.3 mg kg^{-1} + fentanyl 0.1 mg kg^{-1}) 0.33 ml kg^{-1} i.m. Cannulae were inserted into an artery and a vein in the ear. Tracheotomy was performed and the animals were paralysed with pancuronium 4 mg and the lungs ventilated artificially to an airway pressure of 15–20 cm H_2O with 3–4 cm H_2O of PEEP, using 50% nitrous oxide in oxygen. Anaesthesia was maintained by a continuous infusion via the ear vein of Hypnorm 0.1 ml kg^{-1} h^{-1} and pancuronium 1 mg kg^{-1} h^{-1}. Saline 0.9% was also given at 5 ml kg^{-1} h^{-1}, with 3 ml kg^{-1} h^{-1} boluses of hydroxyethyl starch (American Hospital supply) if required to maintain blood volume and arterial pressure. Airway pressure and arterial pressure were measured continuously using Statham pressure transducers and a Devices carrier amplifier with signals recorded on a Devices multichannel recorder.

The animals were allocated to four groups. *Group 1* were controls.

Animals in *group 2* were subjected to osmotic disruption of the BBB with 30 ml of arabinose 1.8 mol $litre^{-1}$ injected slowly over 30 s into the internal carotid artery [5]. This vessel was dissected out and clamps placed on the external carotid artery and the artery to the pinna on the side of injection.

Hypertension was induced in *group 3* animals using an i.v. bolus of angiotensin II, 20 μg kg^{-1} [6]. To potentiate the effects of angiotensin II, the lungs were ventilated during this period with a nitrous oxide in oxygen mixture containing 10% carbon dioxide.

Craniotomy was performed in *group 4* animals and a potassium ion sensitive electrode was inserted 1 mm into the parietal cortex. The electrodes detected the extracellular potassium throughout the course of the study, their signals being processed by a high impedance amplifier and recorded on a Watanabe MC6623 recorder [7]. The potassium electrodes were calibrated [7] using six dilutions of potassium chloride in sodium chloride, to maintain a constant chloride concentration of 150 mmol $litre^{-1}$ and potassium ion concentration of 1, 3, 5, 10, 25 and 50 mmol $litre^{-1}$. The cationic balance was maintained at 150 mmol $litre^{-1}$ with sodium ions. Calibrations were carried out before each insertion into the brain and after termination of the study, the difference in calibrations being approximately 1 mmol $litre^{-1}$. In every case there was a large increase in potassium ion concentration to more than 50 mmol $litre^{-1}$ on final cardiac arrest induced with i.v. potassium chloride. Hypotension was induced with an infusion of trimetaphan 10 mg kg^{-1} h^{-1} i.v., 1% inspired halothane and a variable infusion of sodium nitroprusside (total dose 1.65–6.25 mg kg^{-1}). Fine adjustment was achieved by blood letting (up to 10 ml kg^{-1}). Mean arterial pressure (MAP) was reduced steadily, over a period of 25–30 min, to between 17 and 20 mm Hg. It was then maintained at this value for 15 min. This pressure was that found, by preliminary studies, to produce an abrupt increase in cortical extracellular potassium concentration.

In each group of animals two radiolabelled molecules were used. Red cells were labelled *in vitro* with chromium-51 to quantify the blood volume in tissues sampled at the end of the study. A 10-ml blood sample was taken from each animal at the start of the study and chromium-51, 1 MBq was added with citrate dextrose solution. After 30 min, the blood was centrifuged and the supernatant removed. The cells were washed, resuspended and re-centrifuged three times. The red cells were re-constituted with 0.9% saline to a volume of 10 ml and injected back into the animal, together with $^{99m}TcO_4^-$ 100 MBq 5 min before any experimental manoeuvre. Fifteen minutes after a manipulation was finished, the anaesthetized animal was killed with a potassium injection, a blood sample being taken antemortem. Tissues were removed, weighed and counted in a well counter to quantify chromium-51 and technetium-99m. In each case the $^{99m}TcO_4^-$ count for the tissue sample was corrected for the blood content of each tissue as measured by the

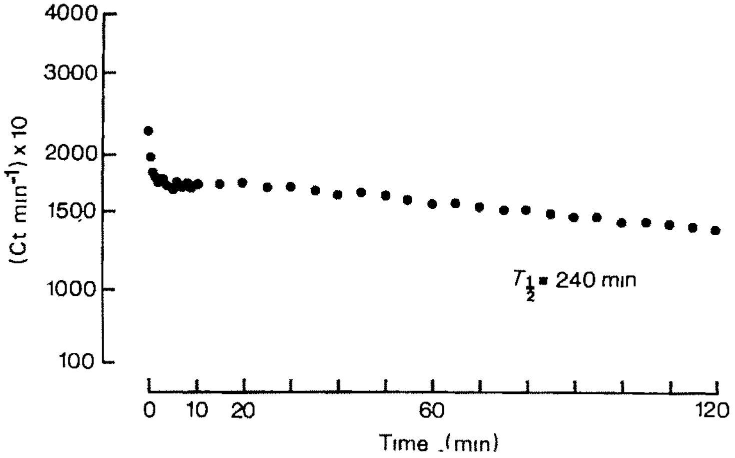

FIG. 1 Typical decay curve for external scintillation counts, over the praecordial region

TABLE I. *Brain:blood partition ratios (×100) for pertechnetate in individual rabbits*

Group	Tissue Left brain	 Right brain
Control		
1	2.8	2.7
2	5.1	5.2
3	3.5	3.4
Osmotic opening of BBB		
1	6.6	16.0
2	13.0	8.6
3	37.8	33.0
Hypertension		
1	3.5	3.1
2	2.5	3.8
3	5.0	2.8
Hypotension		
1	3.8	1.4
2	3.4	4.9
3	2.9	2.8
4	2.1	1.8

chromium-51. A corrected $^{99m}TcO_4^-$ tissue:blood partition ratio was calculated.

Data were analysed using the Randomization test for two independent samples [8].

RESULTS

Clearance of pertechnetate

An external scintillation detector over the rabbit's heart was tuned to detect technetium-99m and this showed a clearance half-life of approximately 4 h (fig. 1).

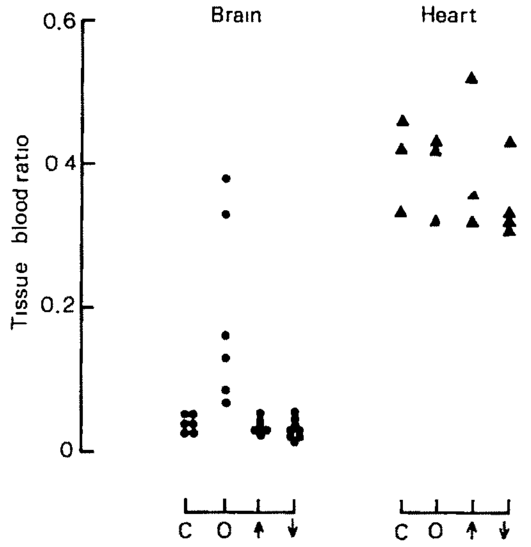

FIG. 2. Pertechnetate tissue:blood partition ratios, corrected for blood content, for brain and heart in the four groups (C = control; O = osmotic opening of BBB; ↑ = hypertension, ↓ = hypotension).

Tissue:blood pertechnetate partition ratios

Blood:tissue partition ratios of $^{99m}TcO_4^-$ in the myocardium showed no differences in any group (fig. 2).

For brain, each hemisphere was sampled separately, so two values for each animal are shown in figure 2 and table I. Significant differences were found, but these should be interpreted with caution because of the multiple comparisons.

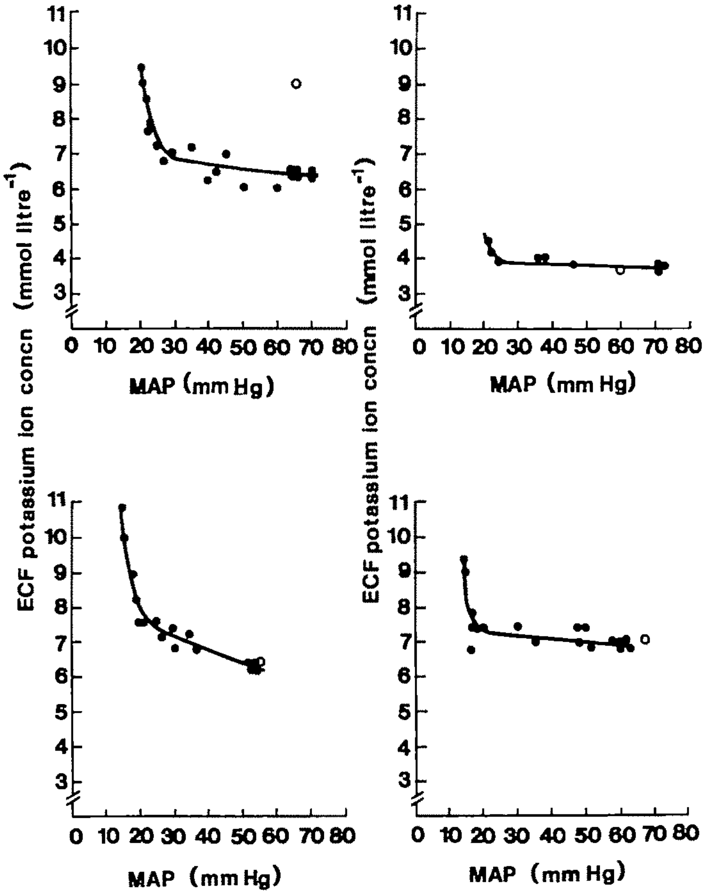

FIG. 3. Cortical extracellular potassium changes plotted against mean arterial pressure (MAP) for four animals. Open circles show values of ECF potassium on returning MAP to normal.

Nevertheless, brain tissue from animals subjected to osmotic damage (group 2) showed a significant five-fold increase in mean brain : blood ratio, each value being greater than control ($P = 0.05$, Randomization test for two independent samples on mean values of left and right brain sample pairs). Compared with control values there was no difference in the partitioning of $^{99m}TcO_4^-$ between brain and blood in the groups subjected to hypertension (group 3) or to hypotension (group 4). In group 3 there was an increase in mean arterial pressure (MAP) from a mean of 70 to a mean maximum of 168 mm Hg.

Ion flux studies in four animals are shown in figure 3. It was necessary to reduce MAP to < 25 mm Hg before a large flux in cortical extracellular potassium occurred. Even so, when potassium flux indicated brain cell injury, there was no change in the partitioning of $^{99m}TcO_4^-$ across the BBB in the group (4) subjected to profound hypotension.

TABLE II. *Tissue : blood partition ratios for pertechnetate in the control group. *One sample only*

Tissue	Mean	Range
Brain	0.04	0.03–0.05
Myocardium	0.40	0.33–0.46
Liver	0.49	0.43–0.56
Kidney	1.02	0.96–1.07
Quadriceps muscle	0.12	0.11–0.14
CSF	0.03*	—
Submandibular	0.56	0.54–0.58
Parotid	0.32	0.18–0.42
Tongue	0.43	0.42–0.45
Skull	0.14	0.10–0.18
Scalp	0.37	0.29–0.44

Other tissues were examined also (table II). The values for liver in the control animals were

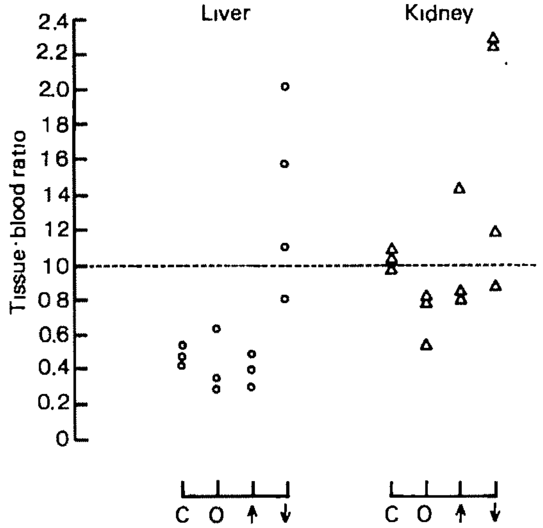

FIG. 4. Pertechnetate tissue:blood partition ratios, corrected for blood content, for liver and kidney in the four groups (C = control; O = osmotic opening of BBB; ↑ = hypertension; ↓ = hypotension).

essentially the same as in the groups subjected to osmotic damage or hypertension (fig. 4). However, the values in the group subjected to hypotension were significantly different from those in the control group ($P < 0.03$, Randomization test for two independent samples), with three of the four values greater than unity.

The kidney showed a wider scatter of values, the hypotension and the osmotic groups showing trends to higher and lower values than controls, respectively (fig. 4). The group subjected to hypotension was not significantly different in view of small numbers and the scatter, but three of the four values in that group were greater than unity.

DISCUSSION

The main finding in this study was that, in contrast with the effect of opening the BBB by osmotic insult, profound hypotension sufficient to produce brain injury did not alter BBB function as measured by partitioning of $^{99m}TcO_4^-$ between brain and blood.

Brain injury was demonstrated at the time of these partitioning measurements by direct measurement of potassium concentrations in cerebral extracellular fluid. This model of cerebral dysfunction has been compared recently with changes in mitochondrial redox activity as an indicator of litre^{-1} of potassium ion did not occur until reduction of cytochrome a, a_3 reached > 80%. Increases in potassium ion > 1 mmol litre^{-1} were associated with complete reduction of cytochrome and reached a mean change of 3.29 (0.1) mmol litre^{-1} [9], similar to those recorded in this study during hypotension.
tension.

The hypotension we achieved also produced no effect on partitioning of $^{99m}TcO_4^-$ in the myocardium, but was sufficient to influence partitioning in the liver and kidney. The mean values in the latter tissues were greater than unity, implying an interference with an active transport mechanism rather than a change in passive diffusion. This may be explained by the greater susceptibility to hypoxia of active transport mechanisms which remove the tracer from liver and kidney cells, compared with the susceptibility of mechanisms which transport it into these cells.

We used angiotensin II to increase MAP as described by Edvinsson and colleagues [6], but in our study hypertension combined with hypercapnia did not influence the partitioning of $^{99m}TcO_4^-$. The mean change in MAP in our study was the same as that reported in rats by this group, but their animals had a greater MAP (180 mm Hg) compared with ours (168 mm Hg). In contrast, they showed that angiotensin II produced an increase in protein leakage into the brain, but demonstrated an even greater protein flux with adrenaline, despite a similar increase in MAP. However, it is unclear whether this represents an increase in permeability of the paracellular pathway or an increase in the transcellular pathway resulting from increased pinocytosis [10].

An explanation of the differences between our study and previous reports is the frequent large percentages of tissue blood content recorded, especially following manoeuvres which might have increased vascular engorgement. Without correcting for the blood content in tissue, we would have shown spuriously high $^{99m}TcO_4^-$ counts resulting entirely from increased blood content, rather than a true increase in partitioning.

In contrast with the effect of hypotension, the osmotic disruption of the BBB produced a striking difference in $^{99m}TcO_4^-$ partitioning, showing that our model was sensitive to changes in BBB function. Our results are consistent with previously published studies on the effects of hyperosmolar solutions in disrupting the BBB [11–13]. A greater increase in tissue $^{99m}TcO_4^-$ in the hemisphere ipsilateral to the intracarotid injection was not a consistent finding, and implies a fairly uniform distribution of arabinose across the circle of Willis. It has been shown that these solutions open the BBB by a non-energy dependent mechanism [13] which is unlikely therefore, to involve pinocytosis. The technique is well established, is reversible and is used in the therapy of human central nervous system malignancies [14].

Our findings conflict with those of Ishikawa and colleagues [2] who showed that hypotension caused either a major breakdown of the BBB with a leak of protein from the intravascular space, or some alteration in a selective active transport system or pinocytosis [10]. The time scale of our study was similar to that in the Ishikawa study, but we found no change in the flux of our much smaller molecule. Furthermore, we also administered Evan's Blue in two preliminary hypotensive experiments, but found no blue staining of the brain in any section. This suggests that there are species differences in addition to different mechanisms of active transport for the various solute molecules crossing the BBB.

$^{99m}TcO_4^-$ is a complex molecule and may behave as a pseudohalide. There is little information on partitioning of $^{99m}TcO_4^-$ between brain and blood. The pulmonary epithelium, although not presenting as formidable a barrier as the BBB to penetration of hydrophilic molecules, has been studied [15] in terms of its permeability to $^{99m}TcO_4^-$ (mol.wt 163 Daltons), chloride and mannitol (mol.wt 160 Daltons). It was found that chloride and $^{99m}TcO_4^-$ had similar permeabilities and that, in penetrating the epithelia, 50 % of each passed through the cell wall and 50 % through the intercellular junctions (paracellular pathway). In contrast, mannitol has a permeability coefficient less than 50 % that of $^{99m}TcO_4^-$ and, as a hydrophilic molecule, it is assumed to pass entirely through the paracellular pathway. These results suggest that, if the impermeability of the BBB to $^{99m}TcO_4^-$ remains intact after hypotension, then so does the impermeability of the BBB for mannitol, explaining its continued efficacy in the management of cerebral oedema under such circumstances. A seven-fold difference in the permeability of the epithelium to $^{99m}TcO_4^-$ has also been reported [15], depending on the direction of movement; that is, permeation from mucosa to serosa is less than in the opposite direction. This demonstrates an active transport system for $^{99m}TcO_4^-$ at least in the pulmonary epithelium.

Sucrose (mol.wt 342 Daltons) and ^{51}Cr-EDTA (mol.wt 341 Daltons), a non-charged hydrophilic molecule, have a low permeation of the BBB similar to that of mannitol [16]. The very low concentration of all these molecules in the brain, even after allowing prolonged periods for diffusion to occur, implies:

(1) A low penetration of the BBB because of greatly impaired diffusion through the paracellular pathway.

(2) An active transport system that is eliminating these molecules from the brain to the blood across the BBB.

(3) Some active transport from the blood to the brain, but a more effective transport system out of the brain at the choroid plexus which removes the tracer.

Active transport mechanisms may be involved in $^{99m}TcO_4^-$ transport in the liver and kidney, and may be affected by severe hypotension. However, in these experiments, severe hypotension did not affect these mechanisms in the brain.

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EFFECT OF HALOTHANE, ENFLURANE AND ISOFLURANE ON BODY TEMPERATURE DURING AND AFTER SURGERY

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SUMMARY

The superficial and deep body temperatures of 40 healthy females undergoing total abdominal hysterectomy were measured during surgery and for 4 h afterwards. The patients were allocated randomly to one of five groups and anaesthetized to produce an end-tidal concentration of 1% halothane, 1% enflurane, 2% enflurane, 1% isoflurane or 2% isoflurane. The patients received also 70% nitrous oxide in oxygen and neuromuscular blockade. The theatre temperature was maintained at 22.0 °C. There were significant body temperature changes during operation in all groups. The mean (SD) decrease in core temperature over 85 min was approximately 1.1 (0.3) °C in the 1% halothane, 2% enflurane and 2% isoflurane groups, and 0.6 (0.4) °C in the 1% enflurane and 1% isoflurane groups ($P < 0.05$). During the recovery period the 1% halothane, 2% enflurane and 2% isoflurane groups took 2 h to rewarm to preoperative temperatures, and the rate of rewarming during this time was similar for all groups.

Heat loss occurs during anaesthesia and surgery. The factors responsible for this are related, not only to the patient, environment or type and duration of surgery, but also to anaesthetic regimen [1]. General anaesthetic agents have central and peripheral effects on body temperature regulation, the alterations being related to the depth of anaesthesia [2].

In this study we have measured the extent of change in body temperature that occurs with different concentrations of halothane, enflurane and isoflurane. In addition, the rate of rewarming during the first 4 h after surgery was measured. We attempted to standardize the operative procedure, the type of patient studied and the environment.

PATIENTS AND METHODS

Forty healthy female patients were studied during total abdominal hysterectomy for menorrhagia. Informed consent was obtained from each patient, and the study was approved by the Hospital Ethics Committee.

Patients who were grossly obese or who had endocrine diseases or pyrexia were not included. None of the patients had previously been exposed to halothane anaesthesia.

Patients were allocated randomly to one of five equal groups. Premedication comprised papaveretum and hyoscine i.m. 60 min before surgery. General anaesthesia was induced with thiopentone. Following the administration of pancuronium, the trachea was intubated and the lungs were ventilated to maintain normocapnia with 70% nitrous oxide in oxygen. Anaesthesia was supplemented with halothane, enflurane or isoflurane. The inspired concentration was adjusted to produce end-tidal concentrations of 1% halothane, 1% enflurane, 2% enflurane, 1% isoflurane or 2% isoflurane respectively, in the five groups, as measured by an anaesthetic gas analyser (Engstrom, Emma). The calibration of the EMMA was checked regularly against known concentrations of certified test gases. The end-tidal anaesthetic concentration was assumed to correlate with the depth of anaesthesia.

All patients received an i.v. infusion of Hartmann's solution 4 ml kg^{-1} h^{-1} during operation and, after surgery, a mixture of 4% Dextrose in 0.18% sodium chloride 40 ml kg^{-1}/24 h. All i.v. fluids were at room temperature. Skin preparation

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comprised 0.5% chlorhexidine in spirit, and drapings of double thickness material were spread over the patient except for the abdomen. No active warming devices were used during surgery. At the end of surgery, each patient was covered with a single sheet and blanket, and transferred to the recovery room, where she remained for 4 h at a mean ambient temperature of 25.0 °C.

Postoperative pain relief comprised an i.m. injection of papaveretum 0.25 mg kg^{-1} when required.

Before induction of anaesthesia, temperature probes were placed against the skin over the lateral aspect of the upper arm, the nipple, the ventral surface of the mid thigh and the lateral aspect of the calf. The temperature was recorded at these sites. Immediately after induction of anaesthesia, a thermocouple probe was inserted under direct vision in the aural canal and well secured with cotton wool to eliminate air currents. Skin and aural canal temperature measurements were repeated at the end of surgery, and subsequently at 30-min intervals for 4 h. The thermocouple probes and the recording thermometer (manufactured by Comark Electronics) were calibrated against a National Physics Laboratory standardized mecury-in-glass total immersion thermometer in a stirred water bath. The probes were accurate to 0.05 °C over the temperature range studied.

Mean skin temperature was calculated using the four-points formula proposed by Ramanathan [3]: mean skin temperature = 0.3 (nipple + arm) + 0.2 (thigh + calf).

Mean body temperature was calculated by averaging mean skin and core (aural canal) temperatures (T) according to the equation of Colin and others [4]: mean body temperature = 0.66 Tcore + 0.34 Tmean skin.

Body heat content (kJ) was calculated and corrected for body weight [5]: mean body heat = mean body temperature × 0.83 × body weight × 4.18, where 0.83 represents specific heat.

The presence or absence of shivering was recorded.

The ambient temperature and the relative humidity in the operating theatre and the recovery room were measured with a mercury-in-glass thermometer and a hair hygrometer, respectively.

Statistical analysis

The temperatures at each time interval studied were grouped and the mean values and standard deviations calculated for each anaesthetic regimen. Student's t test was used to compare observations in the same groups of patients, and the unpaired t test, and Welch's test where appropriate, for comparison among different groups. For each patient, the rewarming rate after surgery was calculated as the slope of the regression line of temperature on the time (every 30 min from 0 to 4 h). $P < 0.05$ was considered significant.

RESULTS

There were no significant differences between the five groups with regard to the patients' physical characteristics, duration of surgery and theatre temperature (table I). The operating theatre relative humidity was maintained at a mean value of 53% (range 49–58%), with 20 air changes per hour. Mean recovery room temperature was 25.0 °C (range 24.0–26.5 °C) and mean relative humidity 54% (range 50–59%). Mean blood loss during surgery was 235 ml (range 205–375 ml), and no blood transfusion was required. During the first 4 h after operation, all patients received one i.m. injection of papaveretum.

Aural canal temperature decreased in all groups by the end of surgery (table II). However, the decrease was significantly greater in those patients with an end-tidal concentration of 1% halothane, 2% enflurane or 2% isoflurane than in those with end-tidal concentrations of 1% enflurane or 1% isoflurane. There was a significant difference between the changes in core temperature in the 2% enflurane and 2% isoflurane groups compared with the 1% enflurane and 1% isoflurane groups. No significant difference was shown between 1% enflurane and 1% isoflurane.

The Minimal Alveolar Concentration (MAC) for the five anaesthetic regimens used in this study and the corresponding core temperature changes are shown in figure 1. At MAC values of 1.3 and 1.5, corresponding to 1% enflurane and 1% isoflurane, respectively, the decrease in aural canal temperature was 0.6 (0.4) °C. At higher MAC, 1.9 for 2% enflurane, 2.0 for 1% halothane and 2.35 for 2% isoflurane, there was a temperature decrease of 1.1 (0.6) °C.

Mean skin temperature decreased in all groups during surgery, with the largest change in the halothane group. However, there was no significant difference between the five groups (table II).

TABLE I. *Mean (range) group characteristics*

	1% Halothane ($n = 8$)	1% Enflurane ($n = 8$)	2% Enflurane ($n = 8$)	1% Isoflurane ($n = 8$)	2% Isoflurane ($n = 8$)
Age (yr)	43 (40–51)	43 (32–61)	46 (30–70)	40 (30–47)	43 (30–51)
Body weight (kg)	64.3 (56–75)	64.6 (55–77)	68 (53–80)	75.5 (63–94)	61.4 (49–80)
Body Mass Index	25.4 (21.9–29.3)	26.9 (22.1–33.5)	26.5 (19.1–32.4)	28.6 (24.1–31.1)	24.9 (22.6–30.5)
Duration of surgery (min)	86 (60–120)	89 (45–115)	81 (55–95)	94 (60–135)	96 (45–135)
Theatre temp. (°C)	21.9 (20.2–22.8)	22.0 (20.3–22.5)	22.2 (20.9–22.8)	22.0 (20.5–23.1)	22.0 (21 5–22.5)
Shivering (No. patients)	3	1	2	2	1

TABLE II. *Mean (SD) intraoperative decrease in aural canal and mean skin temperature (°C). Significant differences* ($P < 0.05$)*:* *v. *halothane*; †v. *1% isoflurane;* ‡v. *1% enflurane*

	1% Halothane ($n = 8$)	1% Enflurane ($n = 8$)	2% Enflurane ($n = 8$)	1% Isoflurane ($n = 8$)	2% Isoflurane ($n = 8$)
Aural canal	1.1 (0.3)	0.6 (0.4)*	1.1 (0.3)‡	0.6 (0.4)*	1.2 (0.4)†
Mean skin	1.2 (0.8)	0.9 (0.7)	1.0 (1.0)	0.5 (0.9)	0.8 (0.9)

Body heat loss (calculated from mean skin and core temperatures) in the halothane group was significantly greater than in the 1% enflurane ($P < 0.05$). No significant difference was found between isoflurane and halothane (fig. 2).

Aural canal temperature (fig. 3) at the end of surgery was significantly lower in the 1% halothane, 2% enflurane and 2% isoflurane groups than in the 1% enflurane and 1% isoflurane groups ($P < 0.01$).

During the first 2 h after operation, all groups had a similar slope of change in temperature (figs 3, 4, table III), but significantly different intercepts ($P < 0.05$). The patients in the 1% halothane, 2% enflurane and 2% isoflurane groups started with lower temperatures and

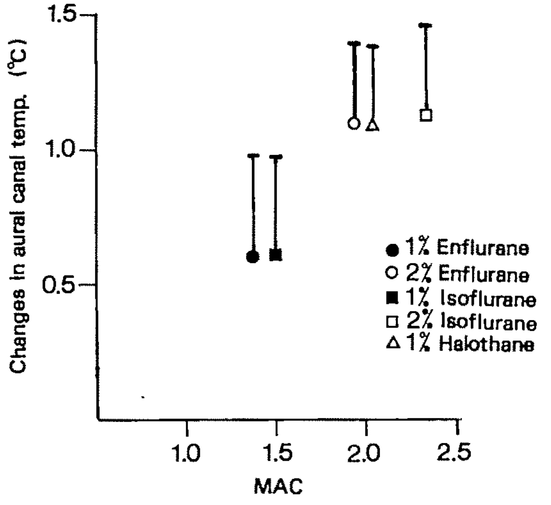

FIG. 1. Aural canal temperature change during surgery with five different MAC values.

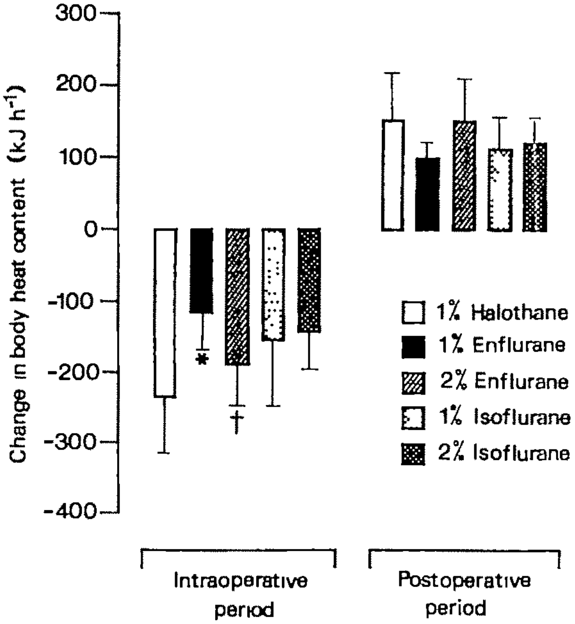

FIG. 2. Intraoperative and postoperative change in body heat content (mean (SD)). Significant differences ($P < 0.05$): *1% enflurane *v.* 1% halothane; †2% enflurane *v.* 1% enflurane.

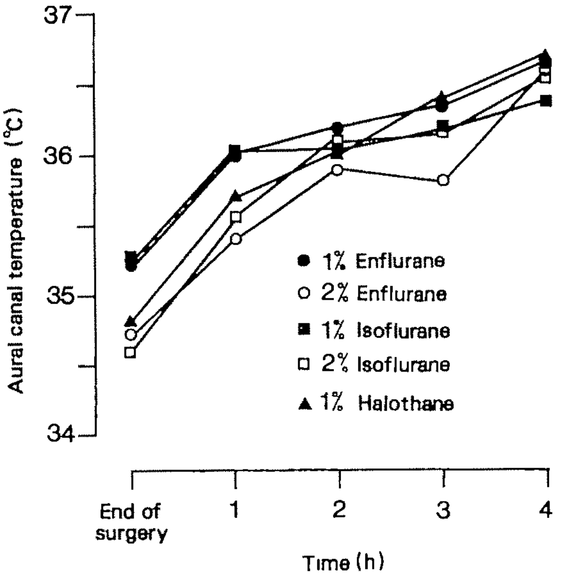

FIG. 3. Postoperative rate of change in aural canal temperature in the five study groups (mean values).

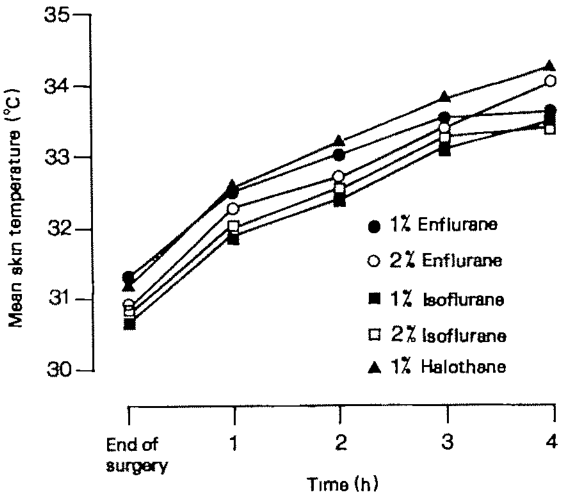

FIG. 4. Postoperative rate of change in mean skin temperature in the five study groups (mean values).

reached preoperative core temperature values within 2 h of the end of surgery, while the 1% enflurane and 1% isoflurane groups rewarmed in 1 h. During the last 2 h of recovery, the rate of change in body temperature was similar for all groups (fig. 4).

Mean heat gain during the recovery period was in the range 101–150 kJ h^{-1} with no significant differences between the groups.

The incidence of post-anaesthetic shivering was greater in the halothane group than the other groups (table I). No correlation was found between shivering and the skin and core temperatures at admission to the recovery room.

DISCUSSION

Core temperature changes occurring during anaesthesia and surgery and in the period immediately after operation varied with end-tidal concentration and not with the particular inhalation anaesthetic agent used.

It is well established that body heat is lost during anaesthesia and surgery as a result of low environmental temperature [6], use of cold i.v. fluids, ventilation of the lungs with cold and dry gases, absence of musle movement [7] and use of drugs [8]. Therefore, it is essential to standardize the operative procedure, the anthropometric characteristics of the subjects, the age group and the environment in order to demonstrate the effect of inhalation anaesthetic agents on body temperature. We chose to study total abdominal hysterectomy because the subjects were relatively young, healthy and fairly lean. In addition, this surgery causes minimal blood loss, and has an average duration of 90 min—sufficient time for major changes in body temperature to occur [9]. The environments in the operating theatre and recovery area were also maintained constant.

TABLE III. *Mean (SD) aural canal temperatures after operation (°C)*

		Time after surgery (h)			
	End of surgery	1	2	3	4
1% Halothane	34.8 (0.6)	35.7 (0.5)	36.0 (0.5)	36.4 (0.5)	36.7 (0.3)
1% Enflurane	35.2 (0.6)	36.0 (0.5)	36.2 (0.5)	36.4 (0.6)	36.7 (0.4)
2% Enflurane	34.7 (0.4)	35.4 (0.7)	35.9 (0.6)	35.8 (0.6)	36.6 (0.6)
1% Isoflurane	35.2 (0.7)	36.0 (0.5)	35.8 (0.7)	36.2 (0.4)	36.4 (0.4)
2% Isoflurane	34.6 (0.7)	35.6 (0.5)	36.1 (0.5)	36.2 (0.4)	36.6 (0.3)

Anaesthetic agents alter body temperature either by depressing heat production or by increasing heat loss. There have been few studies comparing the effect of individual anaesthetic agents on body temperature. Morris [9] did not find any difference between the effect of ether, halothane or methoxyflurane on body temperature during anaesthesia. Engleman and Lockart [10] found in children, that halothane in a nitrous oxide in oxygen mixture produced a greater decrease in rectal temperature than did ketamine. Unfortunately, in that study, the ambient temperature was not controlled well.

Holdcroft and Hall [11] failed to shown any significant difference in heat loss when patients's lungs were ventilated artificially with nitrous oxide in oxygen and supplemented with 0.5% halothane or 1% halothane, or with a moderate dose of fentanyl (10 $\mu g\ kg^{-1}$) for up to 3 h of anaesthesia under standardized conditions. In a study comparing high dose fentanyl (50 $\mu g\ kg^{-1}$) and 1% halothane in non-cardiac patients, the same authors found that fentanyl produced a greater redistribution of body heat from core to periphery than did halothane, and that it caused a greater reduction in aural canal temperature [12]. However, a subsequent study comparing halothane and fentanyl failed to show a different pattern of temperature distribution [13].

The effects on body temperature of enflurane and isoflurane at anaesthetic concentrations have been investigated in volunteers by Stevens and others [14] and by Calverley and others [15]. These authors observed an increase in skin temperature with higher concentrations of the anaesthetic agents. This conflicts with the present study, which showed a reduction in body temperature during surgery with increasing alveolar concentrations. However, in the present study, surgical stimuli, neuromuscular blockade and the exposure of the peritoneal cavity were all important factors which were not present in the other studies.

The reduction in mean skin temperature during surgery showed a wide variation between patients in each group, and did not depend on the drug and the concentration used. It was interesting to observe that halothane caused the largest decrease in mean skin temperature amongst the five groups studied, and this contributed to the greatest loss of body heat. This is in agreement with the observations of Holdcroft and Hall [11].

It is not clear from this study by what mechanism these anaesthetic agents cause different temperature gradients from core to skin. While the effect of halothane on muscle blood flow seems variable [16], with isoflurane there is a great increase in muscle blood flow which appears to be dose dependent [14]. With enflurane there is a decrease in resistance without a change in muscle blood flow [15]. Nevertheless, halothane, enflurane and isoflurane decrease resistance to blood flow in cutaneous vessels, causing heat loss.

During the postoperative period the rate of change in core temperature was similar for 1% halothane, 2% enflurane and 2% isoflurane, and significantly different from 1% enflurane and 1% isoflurane groups. While the last two groups reached a core temperature of 36.0 °C within 1 h from the end of surgery, the other three groups rewarmed to preoperative values after 2 h of recovery, with a large heat gain occurring during the first 1 h after operation.

The clinical implications of these findings are that, by using 1% halothane, 2% enflurane or 2% isoflurane during anaesthesia, body temperature decreases during operation and the postoperative rewarming can be delayed.

Previous studies have shown that the majority of patients who leave the recovery room are still hypothermic [17]. In young healthy patients this might not cause serious clinical problems, but in the elderly and in patients with a poor cardiovascular and respiratory reserve, the high metabolic rate required during rewarming can increase tissue oxygen demand by as much as 400–500% [18].

The rate of change in mean skin temperature during recovery was similar for all groups. They all rewarmed by approximately 1.2 °C during the first 1 h of recovery. This change contributed to a mean heat gain of 200 kJ during this period. However, throughout the recovery period, mean skin temperature in the halothane group was greater by 0.6 °C than that of isoflurane.

Shivering occurred in all groups within the first 1 h, and the greatest incidence occurred in the halothane group. These data are in agreement with earlier findings for halothane [19], while a low incidence of shivering with isoflurane has been reported [20]. More recent work has shown that post-anaesthetic shivering appears not to differ, in character and aetiology, from that occuring with exposure to cold [21].

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SERIAL PEAK EXPIRATORY FLOW RATES IN MOTHERS DURING CAESAREAN SECTION UNDER EXTRADURAL ANAESTHESIA

M. GAMIL

SUMMARY

Peak expiratory flow rate (PEFR) was measured in 19 mothers during elective Caesarean section under unsupplemented extradural anaesthesia. In 18 mothers, serial measurements of peak expiratory flow rate indicated adequate expiratory reserve and residual abdominal muscle power consistent with an effective cough. In one mother, with severe respiratory disease, PEFR decreased to a value indicative of inadequate cough. Data for one other mother who came for emergency Caesarean section after 4 h of an extradural infusion also indicated an inability to cough.

Caesarean section under extradural anaesthesia requires complete bilateral sensory block from T6 to S5 [1]. In addition, inspiratory capacity may be affected by the extradural block and the surgery, both of which may contribute to impairment in the patient's ability to cough effectively [2, 3].

These disabilities must be considered important, since vomiting associated with surgery in such patients varies between 11 and 20% [2, 4]. The conscious patient may aspirate, especially when in the supine position, despite competent laryngeal reflexes [5–8]. It is more difficult to drink fluid from a glass, or to cope with vomit in the mouth, while recumbent. It is also difficult to cough without using the abdominal muscles.

Peak expiratory flow rates have been used to estimate the efficacy of cough in general surgical patients under extradural anaesthesia [9], but not in pregnant patients.

PATIENTS AND METHODS

Nineteen consecutive patients presenting for elective Caesarean section under extradural anaesthesia were invited to join the study. No patient declined. Pre-existing respiratory disease or other systemic disease was not a contraindication to inclusion in the study. A 20th patient was admitted to the study after 4 h of trial labour.

Ranitidine 150 mg was administered by mouth the night before surgery and repeated 2 h before operation; sodium citrate 30 ml was administered by mouth 30 min before operation. Hartmann's solution 2 litre was infused i.v. before the extradural block was performed. The extradural catheter was sited with the patient in the sitting position. The first two-thirds of the estimated dose of 0.5% plain bupivacaine was administered while the mother was sitting and she remained so for 20 min. Further bupivacaine was administered extradurally with the patient in the lateral position as required to produce bilateral sensory block from T6 to S5. Ephedrine, in 10-mg increments, was administered if maternal systolic arterial pressure decreased by more than 10 mm Hg from the preoperative value [10]. Motor block was assessed on the Bromage scale [11], just before the skin incision. The level of sensory block was estimated by testing for detection of cold using ethyl chloride spray. The extradural catheter was removed immediately after surgery, without a further top up.

Peak flow measurements were made using a Mini-Wright Meter [12, 13] (calibrated by the manufacturers) at the following times:

(1) before the block while in the anaesthetic room;

(2) just before incision;

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TABLE I. *Changes in PEFR. †Measurements of peak expiratory flow rates: 1 = preoperative baseline; 2 = before skin incision (extradural block established); 3 = after delivery of the baby before abdominal wall closed; 4 = 30 min after operation, in recovery room; 5 = 48 h after operation; 6 = 6 days after operation. No patient vomited. ***Significantly different from the baseline readings* ($P < 0.001$)

											Peak expiratory flow rate (litre min^{-1})†							PEFR change		
Subject No	Ht (cm)	Wt (kg)	Age (yr)	Baby no	Ht of block	Motor block score	0.5% Bupivacaine (ml)	Ephedrine (mg)	Systolic AP < 100 mm Hg	Nausea	Predicted	1	2	3	4	5	6	1–3	1–5	Comments
No pre-existing respiratory disease																				
1	165	70	31	1	—	I	22	None	No	No	385–470	460	400	310	380	340	450	−150	−120	
2	158	92	28	2	T6	0	25	45	No	Yes	380–465	410	370	340	350	350	410	−70	−60	
3	155	98	25	3	T5	0	23	45	No	Yes	370–455	350	270	260	300	240	320	−90	−110	
4	158	89	30	3	T6	0	25	None	No	No	385–470	410	410	370	370	260	370	−40	−150	
5	170	83	25	1	T5	0	25	6	No	Yes	405–490	370	350	250	370	260	370	−120	−110	
6	153	69	23	1	T5	0	24	30	Yes	Yes	380–465	400	350	330	350	290	360	−70	−110	
7	156	71	24	3	T6	0	20	20	No	No	370–455	380	300	270	280	280	250	−110	−100	
8	163	92	29	2	T6	I	30	9	No	No	380–465	470	430	370	370	330	410	−100	−140	Smoker
9	148	78	23	2	T6	I	22	30	No	No	360–445	510	430	350	350	270	350	−160	−240	
10	158	85	27	1	T5	0	23	30	No	No	375–460	440	400	350	390	270	360	−90	−170	
11	140	59	23	1	T7	I	23	60	No	No	355–440	330	310	280	280	220	340	−50	−110	
12	150	66	27	2	T5	0	21	5	No	No	365–450	450	340	300	340	290	380	−150	−160	Turners Mosaic
13	150	66	39	6	T6	I	20	23	No	No	365–450	320	300	280	280	220	270	−40	−100	Smoker
14	150	73	28	1	T5	0	20	30	No	No	370–455	350	300	260	310	250	270	−90	−100	
15	153	65	30	2	T8	I	24	30	No	Yes	380–465	410	380	315	340	340	370	−95	−70	
16	158	76	26	3	T4	0	27	60	No	No	385–470	460	410	360	395	210	350	−100	−250	
17	145	67	23	4	T4	0	20	60	No	Yes	365–450	310	300	250	250	< 100	200	−60	−210	
Mean	155	76	27	—	—	—	23	28	6%	35%	—	402	356	309***	336	266***	343	−93	−136	
Mode	—	—	—	—	T6	0	—	—	—	—	—	—	—	—	—	—	—	—	—	
SD	—	—	—	—	—	—	—	—	—	—	—	58	52	43	44	61	64	37	55	
Pre-existing respiratory disease																				
18	147	75	30	3	T6	0	20	45	No	No	360–445	170	150	120	180	140	150	−50	−30	Pulmonary TB
19	160	78	22	5	T6	0	22	12	No	No	380–465	300	250	250	270	230	290	−50	−70	Asthma
After 4 h trial labour																				
20	155	100	36	5	T5	III	24+15	9	No	No	380–465	415	360	160	320	260	360	−255	−155	Smoker

(3) after delivery of the baby just before closure of the peritoneum;

(4) in the recovery room, at 30 min after operation;

(5) 48 h after operation;

(6) 6 days after operation.

All measurements were made with the patient in the supine position with one pillow under the head. The highest value of three measurements was recorded [14].

The results were analysed using Students *t* test with adjustment for small numbers and unequal variances [15].

RESULTS

The extradural block was inadequate in one patient presenting for elective Caesarean section and details of the remaining 19 mothers are presented. Two patients (Nos 18, 19) had pre-existing respiratory disease.

All mothers showed consistent reductions in PEFR as the extradural block became established and surgery began (table I). The lowest values were observed after delivery of the baby while the abdomen was still open. The average decrease from baseline until delivery of the baby was -93 litre min^{-1} (range -40 to -160 litre min^{-1}) ($P < 0.001$). There were also significant differences from baseline to the value 48 h after operation when pain limited effort; the average difference was -136 litre min^{-1} (range -30 to -150 litre min^{-1}) ($P < 0.001$).

Mother No. 18 had pulmonary tuberculosis treated with rifampicin and isoniazid. Her baseline PEFR was low (170 litre min^{-1}) and this decreased further with the extradural and surgery to 120 litre min^{-1}. She could not initiate coughing for approximately 60 min. In the recovery room, her PEFR was 180 litre min^{-1} and she was able to clear her secretions and improved symptomatically. At 48 h after operation, her PEFR was 140 litre min^{-1}. Parenteral opioids were restarted to facilitate expectoration, and she recovered well.

Mother No. 20 had received an extradural infusion of bupivacaine 0.375 mg % at a rate of 6 ml h^{-1} for 4 h of a trial of labour before presenting for emergency Caesarean section. Her peak expiratory flow rate decreased from 415 litre min^{-1} to 160 litre min^{-1} and for 15 min she had difficulty initiating a cough to clear her secretions. She was obese and a heavy smoker. In the recovery room her PEFR increased to 320 litre min^{-1} and she recovered well. Peak expiratory flow rate increased by 6 days but did not attain preoperative baseline values.

The incidence of maternal hypotension (systolic < 100 mm Hg) was 5%. Most mothers received ephedrine, but only one had a recorded systolic arterial pressure < 100 mm Hg. There was a 33% incidence of nausea, associated usually with peritoneal traction. No mother vomited.

DISCUSSION

Experience with patients Nos 18 and 20 suggests that a peak expiratory flow rate <200 litre min^{-1} may be associated with inability to initiate a satisfactory cough. It is assumed that there is a critical air velocity which must be achieved before sufficient turbulence can be generated to accelerate mucous or other foreign material towards the glottis. There was a significant reduction in PEFR in all mothers studied but, in the absence of pre-existing repiratory disease, the majority of mothers presenting for elective Caesarean section under extradural anaesthesia may be expected to retain sufficient reserve to be able to cough if necessary.

If impairment of coughing ability is suspected, it would be prudent to avoid sedative supplementation and observe the patient closely for regurgitation. In addition, the patient should not be nursed in the flat supine position in the recovery room until the extradural block has regressed and the mother has sufficient power to turn herself onto her side in the event of vomiting.

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SHORT TERM EFFECT OF NITROUS OXIDE ON METHIONINE AND S-ADENOSYL METHIONINE CONCENTRATIONS

B. D. ROYSTON, T. BOTTIGLIERI AND J. F. NUNN

SUMMARY

Concentrations of methionine and S-adenosyl methionine (SAM) have been measured in various tissues of rats exposed to 50% nitrous oxide for periods up to 80 min, a time by which there is detectable interference with thymidine synthesis in bone marrow. There were no significant changes of either SAM or methionine in plasma, whole blood or brain. Hepatic SAM was unchanged, but there was a highly significant reduction in hepatic methionine, to 62% of control, after 80 min exposure to nitrous oxide.

Exposure to nitrous oxide causes oxidation of vitamin B_{12}, the bound cofactor of methionine synthase (fig. 1). Inhibition of this enzyme occurs very rapidly in the rat, but more slowly in man [1]. In both species, this is followed by inhibition of thymidine synthesis which appears to result from depletion of 5,10-methylene tetrahydrofolate (THF), the obligatory carbon donor for the conversion of deoxyuridine into (deoxy)thymidine.

5,10-Methylene THF is derived from 10-formyl THF which results from the interaction of THF and active formate which is derived from methionine (fig. 1). THF and methionine are the two products of the transmethylation reaction inhibited by nitrous oxide. However, at the present time it is not clear whether the reduction in 5,10-methylene THF is caused by a critical depletion of methionine or THF (or both), or by some other effect of nitrous oxide unrelated to vitamin B_{12} oxidation.

In the rat, inhibition of thymidine synthesis is evident after 1 h of exposure to nitrous oxide [2]. However, liver methionine concentration is 88% of control after 12 h of exposure and 84% after 24 h [3]. Hepatic concentrations of S-adenosyl methionine (SAM) were 70% and 67% of control, respectively, after 2 h and 4 h exposure to nitrous oxide [4, 5]. We are unaware of any measurements of methionine or SAM concentrations in the rat after shorter exposures.

Thus it is unclear whether depletion of methionine or of SAM is critical for interference with thymidine synthesis in the early stages of nitrous oxide exposure. We have therefore examined changes in methionine and SAM concentrations in the rat during the first 80 min of exposure to nitrous oxide, — a time when the deoxyuridine suppression test has already become abnormal.

MATERIALS AND METHODS

Exposure to nitrous oxide

A Perspex exposure chamber was fitted with a trap door through which rats could be introduced into the chamber without appreciable change in its gas composition. The chamber (30 litre capacity) was flushed with at least 100 litre of a 50% mixture of nitrous oxide in oxygen (Entonox) and flow was then maintained at 7 litre min^{-1}. Batches of six specific pathogen-free Sprague–Dawley male rats were exposed for 5, 10, 20, 40 or 80 min. Cage controls breathed air: chamber controls (80 min) breathed either air or 50% oxygen in nitrogen. The use of the various control groups is indicated in table I. Humidity in the chamber did not increase above 50% and carbon dioxide concentration above 0.2%. At the specified time, rats were removed from the chamber and immedi-

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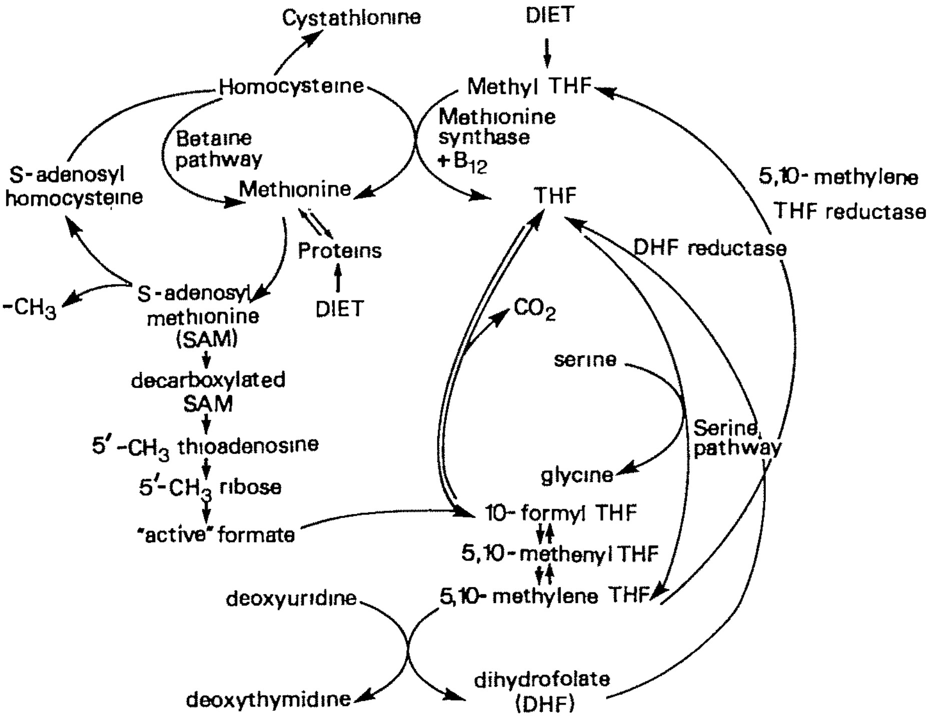

FIG. 1. Metabolic pathways linking the synthesis of methionine and deoxythymidine.

TABLE I. *Concentrations of methionine and S-adenosyl methionine (SAM) (mean (SD)). *Differs from pooled controls (P < 0.0005)*

	Plasma			Liver		
	Methionine (μmol litre^{-1})	SAM (nmol litre^{-1})	Blood SAM (nmol litre^{-1})	Methionine (nmol g^{-1})	SAM (nmol g^{-1})	Brain SAM (nmol g^{-1})
Controls						
Cage air	48.9 (2.7)	—	—	28.3 (6.0)	55.3 (8.5)	17.7 (3.1)
Chamber air	—	—	—	24.5 (4.7)	53.5 (11.5)	—
Chamber 50% O_2 50% N_2	47.3 (4.0)	127 (34)	4022 (342)	22.2 (2.6)	49.8 (7.0)	17.6 (4.4)
Nitrous oxide exposure						
5 min	48.0 (5.7)	174 (55)	4362 (262)	—	53.5 (12.5)	—
10 min	44.3 (5.3)	108 (35)	3787 (1505)	—	59.8 (9.5)	—
20 min	43.6 (4.6)	144 (41)	4395 (547)	—	62.5 (7.5)	—
40 min	43.1 (10.2)	139 (27)	4218 (1027)	—	50.8 (12.3)	16.9 (2.2)
80 min	50.2 (9.2)	138 (52)	3892 (545)	15.5 (2.5)*	50.5 (10.3)	15.2 (2.3)

ately given a lethal i.p. dose of pentobarbitone 60 mg kg^{-1}. As soon as consciousness was lost, the rats were exsanguinated by cardiac puncture and portions of the liver and brain were removed. Hepatic methionine was measured only in controls and after 80 min exposure.

Storage and analysis of samples

Whole blood and plasma were deproteinized with 7 and 2 volumes of perchloric acid 0.48 mol litre^{-1}, respectively. For analysis of SAM, liver and brain tissue were deproteinized with 10 and 5 volumes of perchloric acid 0.8 mol litre^{-1}, respectively. The supernatants were stored at −20 °C. For methionine analysis, liver tissue was immediately deproteinized with 10 volumes of methanol and the supernatants stored at −20 °C.

SAM concentrations were measured by a modification of the enzymatic double isotope method of Giulidori and Stramentinoli [6]. Methionine was determined by high pressure liquid chromatography on a 25-cm hypersil octadecylsilyl column. Detection was by fluorescence after derivatization with o-phthaldialdehyde. In our hands, the limit of detection was 2 μmol litre^{-1} and the coefficient of variation for replicate samples was 7.4%. The techniques are described in detail elsewhere [7], except that a fluorescent detector was used with the high pressure liquid chromatography. All samples were arranged randomly for analysis.

Statistical analysis

One-way analysis of variance was used to test the significance of differences of means of more than two exposure groups. Unpaired Student's *t* tests were applied to the mean values for pairs of different exposure groups.

RESULTS

Plasma

Plasma methionine concentrations (fig. 2, table I) showed no significant differences between either of the two control groups and any of the exposed groups. Cage controls for plasma concentrations of SAM were not available, but there were no significant differences between the chamber controls and any of the exposed groups (fig. 2, table I).

Whole blood

Whole blood concentrations of SAM showed no significant differences between chamber controls and any of the exposed groups (fig. 2, table I).

Liver

Analysis of variance showed no significant differences in methionine concentrations between any of the three control groups ($P = 0.147$) (table I). All three control groups were pooled, giving a mean methionine concentration of 25.0 nmol g^{-1}. Following 80 min exposure to nitrous oxide the mean methionine concentration was 15.5 nmol g^{-1}, the difference from pooled controls being highly

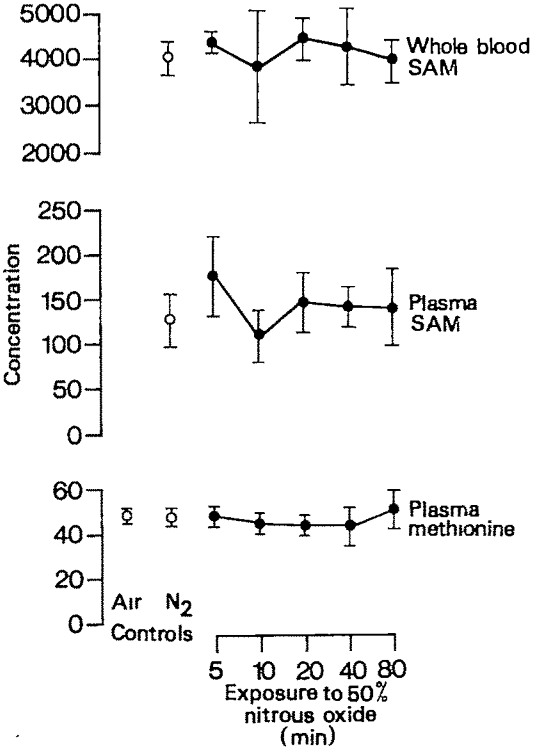

FIG. 2. Blood and plasma concentrations (nmol litre^{-1}) (mean, 2SEM) of SAM and plasma methionine concentrations (μmol litre^{-1}) during 80 min exposure to 50 % nitrous oxide, compared with cage controls exposed to air and chamber controls exposed to 50 % nitrogen in oxygen (N_2).

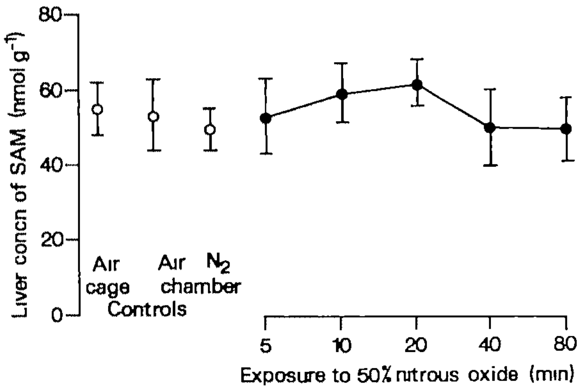

FIG. 3. Liver concentrations (mean, 2SEM) of SAM during 80 min exposure to 50 % nitrous oxide, compared with cage controls exposed to air and chamber controls exposed to air or 50 % nitrogen in oxygen (N_2).

significant ($P < 0.0005$). Each separate control group was also significantly different from the group exposed to nitrous oxide.

There were no significant differences in SAM concentrations between cage and chamber controls breathing either air or 50% nitrogen in oxygen (table I, fig. 3). All three control groups were pooled, giving a mean SAM concentration of 53.3 (SEM 1.85) nmol g^{-1}. The SAM concentrations in no group exposed to nitrous oxide were significantly different from the pooled controls.

Brain

There were no significant differences in SAM concentrations between cage and chamber controls (table I). These two groups were pooled to give a mean SAM concentration of 17.6 nmol g^{-1}. Both the exposed groups showed no significant difference from the pooled controls.

DISCUSSION

We have found no change in plasma methionine or SAM concentrations in both plasma and blood during exposure to nitrous oxide lasting up to 80 min. Lumb and colleagues [3] found plasma methionine concentration was 64% of control after 24 h exposure of the rat to 50% nitrous oxide. Vinã, Davis and Hawkins [8] found an insignificant reduction to 82% of control after 24 h exposure. We are unaware of any measurements of plasma concentrations of SAM in the rat exposed to nitrous oxide. Our results may be compared with our own human data which showed no change in plasma concentrations of either methionine or SAM during nitrous oxide anaesthesia lasting between 25 and 217 min [7].

We have shown a highly significant reduction of hepatic methionine concentration to 62% of pooled control values after 80 min exposure to nitrous oxide. This may be compared (fig. 4) with reductions to 88% of control after 12 h [3] and, after 24 h exposure, reports of 84% [3] and 55% [8]. Lumb and colleagues [3] found values tending back towards normal during exposures lasting 8 days (fig. 4).

In contrast, our values for hepatic concentrations of SAM in the rat showed no significant reduction below control values during 80 min exposure to nitrous oxide. This may be compared (fig. 4) with reductions into the range 65–70% of control, reported for 2 h exposure [5] and 4 h exposure [4]. A progressive decline in hepatic concentration of SAM has been reported [3] between 12 h and 10 days of exposure to nitrous oxide. We are unaware of any human data for hepatic changes in methionine or SAM concentrations following exposure to nitrous oxide.

S-Adenosyl methionine (SAM) is formed only from methionine, but the kinetics of the two

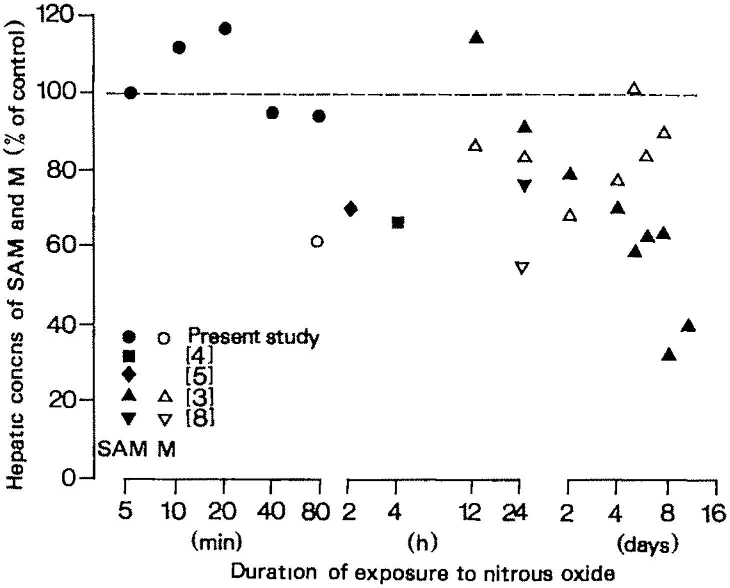

FIG. 4. Comparison of studies of hepatic methionine (M) and SAM concentrations during exposure of rats to nitrous oxide.

hepatic iso-enzymes of methionine adenosyl transferase ensure the maintenance of SAM concentrations in the face of low methionine concentrations. SAM is maintained well in the early stages of starvation and plasma concentrations were unaffected by the reduction in plasma methionine following preoperative restriction of feeding [7].

It would appear that plasma methionine concentrations do not reflect hepatic methionine concentrations in the early phases of exposure to nitrous oxide. For haemopoiesis, the relevant tissue is bone marrow, but there are severe technical difficulties in measuring the methionine concentration in marrow stem cells. Inferences may be drawn from hepatic intracellular concentrations of methionine and SAM. However, the possibility remains that the interference with thymidine synthesis in marrow may result from critical depletion of SAM in marrow stem cells, not reflected in other tissues.

By the time thymidine synthesis is measurably impaired, after approximately 1 h of exposure to nitrous oxide, SAM concentrations in liver, brain and plasma are still normal. Since SAM is an intermediate between methionine and active formate (fig. 1), there seem no grounds for believing that reduction of methionine concentration plays any part in the deficiency of 5,10-methylene tetrahydrofolate, which decreases to 27% of control after exposure of rats to nitrous oxide for 4 h [4].

If depletion of methionine and SAM are not factors in early impaired thymidine synthesis (detectable after 1 h of exposure to nitrous oxide in the rat [2] and as little as 2 h in man [9, 10]), there are two other possibilities. The first is depletion of tetrahydrofolate according to the classical theory of the "methyl folate trap". Eells and colleagues [4] reported tetrahydrofolate significantly reduced from 14.2 to 8.5 nmol g^{-1} in rats after 4 h exposure to nitrous oxide. The second possibility is that nitrous oxide may interfere with entry of tetrahydrofolate into the cell and the formation of folate polyglutamates [11, 12].

The deoxyuridine suppression test may remain abnormal for as long as 6 days following 24 h exposure to nitrous oxide [9]. Megaloblastic anaemia develops in man [13, 14] and fetotoxicity occurs in the rat [15], both effects being at least in part reversible with administration of 5-formyl THF (folinic acid, converted in the body to 10-formyl THF). This accords with the direct observation [4] that 10-formyl THF was reduced to 29% of control following exposure of rats to 50% nitrous oxide for 4 h, although this large change did not achieve statistical significance. However, the precise mechanism by which this results from inhibition of methionine synthase activity is still not clear. It seems unlikely that SAM depletion is responsible in the early stages, but depletion of hepatic SAM has been clearly shown after several days exposure to nitrous oxide [3] (fig. 4). Thus the biochemical mechanism of depletion of 5,10-methylene THF may be different for different durations of exposure to nitrous oxide.

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SOLUBILITY OF FREON-22 IN BLOOD AND LUNG TISSUE

P. J. FRANKS, R. H. HOOPER AND P. R. M. JONES

SUMMARY

Despite the frequent use of freon-22 (e.g. to measure pulmonary blood flow), there is no agreement on its solubility in water or body fluids. The values in the literature vary, often quoted without reference to measurement or identification as Ostwald or Bunsen coefficients. We used a Scholander apparatus and determined the Bunsen solubility coefficient ($ml_{gas}.(ml_{fluid}.$ atmosphere$)^{-1}$) at 37 °C as: 0.476 in water; 0.673 in human whole blood; 0.479 in human plasma; 0.662 in canine whole blood; 0.437 in canine plasma; and 1.077 in homogenized canine lung tissue. As pure freon was used, these solubilities may not be applicable if freon-22 does not obey Henry's law. In man, the Ostwald solubility coefficient is calculated as 0.76 ml/ml whole blood at BTPS. These results provide information for further studies involving freon-22, and clear the confusion which has arisen from poorly defined solubility coefficients.

Over the past 20 years freon-22 has been used for the inert gas method of measurement of cardiac output. A major drawback to its use is the confusion between Bunsen and Ostwald solubility coefficients; the exact coefficient is critical for an accurate determination of cardiac output.

Several studies report values for solubility coefficients, although none indicates how the measurements of solubility were performed, or their accuracy. Bayley, Clements and Osbahr [1] used a coefficient of 0.71 $ml_{gas}.(ml_{fluid}.$atmosphere$)^{-1}$ at 37 °C (which will be represented as ml ml^{-1} $atmos^{-1}$) determined in rabbit blood. A value of 0.74 ml ml^{-1} $atmos^{-1}$ at 37 °C in neonatal blood was given in another paper [2]. These values are confusing, as it is unclear whether the gas volumes were corrected to STPD (Bunsen coefficients) or to BTPS (Ostwald coefficients). Both these studies failed to provide experimental details of the solubility measurement.

The solubility coefficient for freon 22 (given in [2]) was attributed to Eger and Shargel, but no information was provided. It was stated that they used an adaptation of the Schölander apparatus [3], and exposed blood to pure freon (J. A. Clements, personal communication). Kruhöffer [4] reported, in an abstract, a Bunsen coefficient of 0.71 ml ml^{-1} $atmos^{-1}$, although the method of determination was prone to inaccuracy (P. W. Kruhoffer, personal communication). Since then, other determinations by that author have fallen within the range 0.62–0.74 ml ml^{-1} $atmos^{-1}$, on exposing blood to pure freon-22. In two later studies the solubility coefficient was 0.73 ml ml^{-1} $atmos^{-1}$ [5,6]; both appear to be Bunsen coefficients, despite the latter paper using the symbol λ, which normally denotes Ostwald solubility coefficients.

The purpose of this study was to examine the solubility of freon-22 in water, blood and lung tissue in order to clear the confusion which has arisen from the application of different solubility coefficients.

METHODS

We used the Schölander apparatus as described elsewhere [3]. This is a relatively simple procedure which requires the calculation of volume uptake of pure freon-22 by a blood sample of a known volume at a known pressure at 37 °C. The Ostwald solubility coefficient (λ) can be determined:

$$\lambda = V_g.(V_B.P_g)^{-1}$$

where V_g is volume uptake of gas (ml), V_B is the volume of blood (ml) into which the gas dissolves

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and P_g is the pressure of the gas (standard atmosphere).

The equations also correct for water vapour pressure [3]. The Bunsen solubility coefficient can be calculated by correcting the difference in temperature using the multiplication factor 0.88 (273 divided by 310).

Purity of freon-22

For this method it is important that the soluble gas sample is either pure, or its proportion in a mixture with an insoluble gas is known precisely. To test the purity of the gas used, a sample was taken from a cylinder of 100% freon-22 (BOC Ltd). The gas was passed through a Pye 104 chromatograph with a molecular sieve 5A and a column of Chromasorb 102 which is suitable for the detection of nitrogen and oxygen. The same volume of air was used as a calibration gas. The output was amplified ×20 for the freon sample. To calculate the percentage of these gases in the sample, the peaks were carefully cut from the chart recorder output and weighed (table I).

As the nitrogen:oxygen ratio demonstrates, there was a small amount of air contaminating the freon-22. The overall purity of the freon-22 was 99.31% after allowing for the small amount of air in the sample (including a calculated value for argon). We assumed that the air caused no interference with the uptake of freon-22 by blood, other than by the reduction of freon partial pressure caused by nitrogen (the minute volume of oxygen would be absorbed by the haemoglobin). Hence, freon partial pressure (P_f) was taken to be 0.995.

Preparation of materials

Twenty millilitre of venous blood was taken from seven human subjects and six dogs and transferred to heparinized tubes, which were rocked gently before storage overnight at 4 °C. Haematocrit was determined (an average of three measures) in each sample and 10 ml was spun down to obtain plasma.

TABLE I. *Percentage of gases in air and freon determined by chromatography*

Gas	Air	Freon-22
N_2 (%)	78.04	0.540
O_2 (%)	20.93	0.145
Total (N_2+O_2)(%)	98.97	0.685
N_2:O_2 ratio	3.73	3.72

The dogs were killed and the lungs removed. The animals had received heparin just before death, to enable blood to drain from the major vessels. It was assumed that any blood remaining in the lung tissues would collect in the capillary bed, and would consequently contribute to the overall solubility of freon-22 in the tissue sample. After storage for 12 h at 4 °C, approximately 3 g of lung tissue was removed from various sites. Care was taken to exclude any of the visible hilar structures, and the samples were weighed. A mass of water, approximately 10 times the lung tissue mass, was added and the whole re-weighed. This was found to be the minimum dilution possible to produce a liquid homogenate suitable for use with the Schölander apparatus. The sample was homogenized until all traces of solid had disappeared. Solubility of freon-22 was measured in this sample by the same method as that used for blood, described below.

The samples were degassed. Each was transferred to a small conical flask with several glass beads and placed in a water bath at 37 °C (solubility in water was also measured at 20 °C), the temperature used for determinations. Highly insoluble gases (argon or helium) were humidified at the test temperature in a water trap and blown continuously over the samples. Air contamination was avoided by use of an enclosed unit submerged in the water bath. The insoluble gas was vented through the water bath to air after it had traversed the conical flask. The flask was shaken vigorously during degassing. As this degassing procedure is less efficient than the rotating tonometer, 4 h was required to clear all traces of oxygen and carbon dioxide from the sample. The haematocrit was checked following degassing to confirm that neither haemolysis nor drying had occurred. The same degassing procedure was used for lung tissue and plasma.

The procedure using the Schölander apparatus was identical to that described by Saidman [3]. After each determination the reaction chamber was washed at least three times with distilled water. This was particularly important when analysing blood, as the red cells adhered to the side of the chamber, making further measurements liable to inaccuracy.

The measurements of solubility were repeated six times on each sample.

Calculations

The calculation of the Bunsen solubility coefficient was identical to that described by Saidman [3], with conversion from the Ostwald coefficient using the multiplication factor described above.

Calculation of the Bunsen solubility coefficient in red cells (α_R) was:

$$\alpha_R = \alpha_B \frac{(100)}{\text{Hct}} - \alpha_P \frac{(100-\text{Hct})}{\text{Hct}}$$

where α_B = solubility in whole blood, α_P = solubility in plasma, Hct = haematocrit.

Calculation of solubility in lung tissue (α_L) was:

$$\alpha_L = \frac{\bar{\alpha}_{tot}.M_{tot} - \alpha_w.M_w}{M_L}$$

where M_{tot} = total mass of diluted homogenate, $\bar{\alpha}_{tot}$ = mean solubility of diluted homogenate, M_L = mass of lung tissue, M_w = mass of water, α_w = solubility in water.

Results were analysed using a one-way analysis of variance for data with one criterion of classification [7]. The symbol V_B is the variation in sample quality, indicating inter-sample variation. Within group variation is given by V_s (variance of experimental error), calculated from the six repeated measures.

RESULTS

In one of the seven human subjects, no measurement was made in plasma; in another none was made in whole blood. Hence there are only five results for human red cells (table II). In the dog, blood was collected from various sites following death. In three of the six samples there was some cell fragmentation, making it impossible to determine haematocrit or plasma separation, but these results have been included in the results for whole dog blood.

We found that the Bunsen solubility coefficient of freon-22 in blood was approximately 0.67 ml ml^{-1} atmos^{-1} for the human and 0.66 ml ml^{-1} atmos^{-1} for the dog. The variance estimates were similar for both.

DISCUSSION

Our freon-22 solubility value is somewhat lower than that reported previously, but there are uncertainties concerning the source of the earlier data. If the value of 0.74 ml ml^{-1} atmos^{-1} used in a previous study [1] refers to the Ostwald solubility coefficient of this gas, the Bunsen coefficient would have been 0.65 ml ml^{-1} atmos^{-1}.

In a comparative study [8] using two gases for rebreathing experiments in man, a Bunsen coefficient of 0.74 ml ml^{-1} atmos^{-1} was used, as suggested by Kruhoffer to these authors in a personal communication. They found that freon-22 significantly underestimated cardiac output compared with an acetylene rebreathing method. They showed that the cardiac output values corresponded very closely to each other if the freon-22 solubility was taken as 0.67 ml ml^{-1} atmos^{-1}. It is

TABLE II. *Solubility of freon-22 in man and dog tissues.* n = *No. samples (each was measured six times and the average value used, except water)*; α = *Bunsen solubility coefficient* (ml_{STPD} $(ml.atmos)^{-1}$); *CV% = coefficient of variation of repeated measures*; *Hct = haematocrit*; V_B = *estimate of variance of sample quality*; V_s = *estimate of variance of experimental error.* **In this study only three of the six samples were free from fragmentation. The mean haematocrit is based on these data only*

	Temp. (°C)	*n*	$\bar{\alpha}$	CV%	$V_B \times 10^{-5}$	$V_s \times 10^{-5}$	Hct (%)
Water	20	10	0.793 (SD 0.011)	1.5	—	—	—
	37	10	0.476 (SD 0.007)	1.5	—	—	—
Whole blood							
Human	37	6	0.673	—	8.82	13.8	45
Dog	37	6	0.662	—	2.78	16.1	49*
Plasma							
Human	37	6	0.479	—	7.23	12.8	—
Dog	37	3	0.437	—	2.33	11.0	—
Red cells							
Human	37	5	0.899	—	—	—	—
Dog	37	3	0.890	—	—	—	—
Lung tissue							
Dog	37	6	1.077	—	818	1074	—

interesting to note that this is the same as the value we found by measurement of the Bunsen solubility coefficient in human blood. It is possible that the value suggested by Kruhoffer was an Ostwald and not a Bunsen coefficient.

Whatever the errors involved in measurements of cardiac output in man involving gas uptake measurements and using the lungs as tonometers, our evidence suggests that the hypothetical value devised by Bonde-Petersen was correct and supports the use of freon-22 in place of acetylene for indirect measurement of cardiac output.

The value obtained in plasma was similar to that found in water at the same temperature, although the solubility in red cells was significantly higher ($t = 13.7$, $P < 0.001$; ratio 0.54:1). This may be a result of high lipid solubility, or of binding with haemoglobin. The solubility in red cells is similar in man and the dog, but a species difference in haematocrit leads to different whole blood solubilities.

As we used methods given elsewhere [3] to achieve comparability, the conditions did not mimic the situation *in vivo*. In particular, the blood was degassed, leading to lack of oxyhaemoglobin and an increased pH. It is possible that both factors could alter freon uptake. Further, we used pure freon, as did the previous workers. It is not known if freon-22 obeys Henry's law and so its use at low concentrations for blood flow measurement may be questionable.

Human cardiac output has been measured by estimating pulmonary blood flow using gases such as acetylene and nitrous oxide. These gases have a whole blood:lung tissue solubility ratio of approximately unity [9]. For freon-22 this is not the case, the ratio being 0.61:1.00 in the dog. The whole blood:red cell solubility ratio is slightly greater (0.74:1.00). It is not clear why lung tissue should have such a high solubility coefficient. Unfortunately, there was considerable variation in the measurement of freon-22 solubility in lung tissue samples (table II). This might have resulted from the degree of dilution of the homogenate necessary for success when using the Schölander apparatus.

The measurement of blood flow through the lungs would not be affected seriously by this inaccuracy. The lung tissue volume is small compared with the alveolar gas volume and the total flow of blood through the lungs over the period of measurement. Consequently, the calculation of pulmonary blood flow should not be compromised seriously by this degree of variation in the tissue solubility measurement.

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PRETREATMENT WITH PARACETAMOL INHIBITS METABOLISM OF ENFLURANE IN RATS

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SUMMARY

We studied the interaction between paracetamol (acetaminophen U.S.P.) and enflurane. Sixteen rats were assigned to four groups (n = 4) to receive: paracetamol 7.5 mg/100 g body weight; paracetamol plus 1% enflurane; 1% enflurane alone, or no treatment (controls). Animals were killed 6 h later. A second series of 16 were treated identically, but were killed after 24 h. Measurements were made of fluoride concentrations in serum, liver and urine (indicators of biotransformation of enflurane), paracetamol concentrations in urine, pathological changes in liver samples, and concentrations of the enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in serum. Pretreatment with paracetamol significantly decreased urinary fluoride at 6 and 24 h after exposure to enflurane, but decreased fluoride concentrations in serum and liver only at 6 h after exposure to enflurane. Paracetamol concentrations in urine did not change after exposure to enflurane. Exposure to paracetamol alone increased AST and ALT. At 24 h after exposure to enflurane, serum concentrations of enzymes in rats pretreated with paracetamol were similar to those of control rats. Pretreatment with paracetamol may therefore inhibit metabolism of enflurane. Although no hepatic damage was observed, the increased in AST and ALT suggested subclinical liver damage in rats given only paracetamol.

Enflurane is a widely used anaesthetic agent generally believed to be safe [1]. It is a substrate of the mixed function oxidase system in the liver [2–8] and has a degree of metabolism of approximately 2% [9]. Fluoride concentrations in serum, liver and urine are used as indicators of its biotransformation [1].

Paracetamol is a commonly used antipyretic analgesic drug that is generally safe in therapeutic doses [10]. It is eliminated mainly by conjugation to the metabolites paracetamol glucuronide and sulphate. A small portion is metabolized by the liver microsomal enzyme system to form reactive metabolites that are inactivated by conjugation with reduced glutathione. If the amount of reduced glutathione is depleted, these reactive metabolites bind covalently to the macromolecules of the liver cell, thereby producing liver cell damage and necrosis [11–13].

This study has investigated the effect of pretreatment with paracetamol (acetaminophen U.S.P.) on biotransformation of enflurane.

MATERIALS AND METHODS

Treatment groups

Sixteen male Sprague–Dawley rats (300 (SEM 50) g) were allocated to four equal groups. The first group of rats were given paracetamol 7.5 mg/100 g body weight per day by mouth for five consecutive days. The second group received this regimen plus, 15 min after the last dose, exposure to 1% enflurane for 2 h. The third group was only exposed to 1% enflurane for 2 h. The fourth group consisted of untreated controls. The animals were placed in metabolic cages for 6 h for collection of urine, after which time they were placed in a chamber containing carbon dioxide to produce anaesthesia. After removal from the chamber for blood sampling by intracardiac

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puncture, they were returned to the chamber to be killed [14, 15]. The same procedure was repeated on 16 other rats, except that these animals were kept in metabolic cages for 24 h instead of 6 h. Samples of urine, blood and liver tissue were taken for analysis and examination.

Administration of drugs

A solution was prepared by dissolving 600 mg of paracetamol in 30 ml of distilled water containing 1 % ethanol. Paracetamol 7.5 mg/100 g body weight was given via a No. 18 feeding needle. Groups not treated with paracetamol were given distilled water by the same method.

Rats treated with enflurane were exposed to the anaesthetic in a 420-litre chamber at 23 (SEM 1) °C. To achieve a concentration of 1 % enflurane, enflurane 31.0 g was vaporized inside the chamber. Chamber samples were taken at 15-min intervals, to confirm the concentration of enflurane by gas–liquid chromatography. Control animals were placed in similar chambers without enflurane.

Analyses

Serum concentrations of the enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured by the University Hospital Clinical Pathology Laboratory [16, 17].

Serum fluoride concentration was determined at 6 or 24 h after exposure to enflurane. One millilitre of serum was added to 1 ml of total ionic strength adjusting buffer. Fluoride ion was determined using an ion selective electrode (the Orion Combination Electrode). A standard curve was prepared from samples containing sodium fluoride 0.01–1.0 $\mu g\ ml^{-1}$ with zero adjustment set at 0.01 $\mu g\ ml^{-1}$ [18]. The fluoride standard curve was linear when plotted on a semilogarithmic scale, fitting with a coefficient of correlation of 0.99.

Urinary fluoride concentration was determined using an Orion Combination Electrode. One millilitre of urine was added to 1 ml of total ionic strength adjusting buffer. A standard curve was prepared from samples containing sodium fluoride 1–100 $\mu g\ ml^{-1}$, with zero adjustment set at 1.0 $\mu g\ ml^{-1}$ [19]. A standard curve was linear when plotted on a semilogarithmic scale fitting, with a coefficient of correlation of 0.99.

Urine concentrations of paracetamol were measured as described elsewhere [20, 21]. A standard curve was linear at 0–500 $\mu g\ ml^{-1}$, with a coefficient of correlation of 0.99.

Histopathology

Liver samples were examined histologically by the University Clinical Pathology Laboratory.

Data are presented as mean values (SEM). Data were analysed by one-way analysis using a log transformation of data. Turkey's studentized range test and Scheffes's test were used for multiple comparison of each pair of treatment groups. $P < 0.05$ was regarded as significant [22, 23].

RESULTS

The concentration of enflurane in the chambers remained at 1.02 (0.01) %. At 6 h after exposure to enflurane, fluoride concentrations in serum and liver samples were significantly greater in animals exposed to only enflurane than in animals pretreated with paracetamol before exposure to enflurane (figs 1, 2). Also, the concentration and total amount of fluoride in urine and in the whole body were significantly greater in the animals exposed only to enflurane than in animals pretreated with paracetamol and exposed to enflurane (table I). By 24 h after exposure to enflurane, fluoride concentrations in serum and liver had returned to control values (serum 40 (10) $ng\ ml^{-1}$; liver 38 (13) $ng\ ml^{-1}$). However, the concentration and total amount of fluoride in urine and in

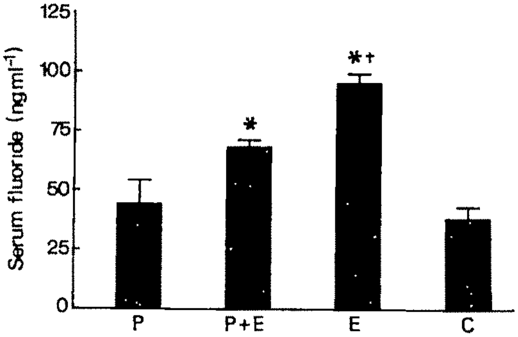

FIG. 1. Fluoride concentrations in serum 6 h after 16 rats were given paracetamol 7.5 mg/100 g body weight only (P); pretreatment with paracetamol and exposure to 1 % enflurane (P+E); 1 % enflurane only (E) or no treatment (controls) (C). Significant differences ($P < 0.05$): *compared with the two groups not given enflurane; † compared with group pretreated with paracetamol and exposed to enflurane.

TABLE I. *Mean (SD) values for fluoride in urine 6 h after exposure of rats to enflurane. Significant differences* ($P \leqslant 0.01$): ** *compared with two groups not given enflurane;* †† *compared with group given paracetamol and enflurane*

Treatment	Volume of urine (ml)	Concentration of fluoride ($\mu g\ ml^{-1}$)	Total fluoride (μg)	Fluoride per body wt ($ng\ g^{-1}$)
Paracetamol	2.3 (0.7)	4.4 (0.4)	12.4 (2.7)	36 (5)
Paracetamol + enflurane	3.0 (0.2)	20.6 (1.9)**	61.7 (5.0)**	175 (12)**
Enflurane	2.8 (0.2)	33.0 (0.8)**††	90.8 (7.6)**††	290 (32)**
None (controls)	3.2 (1.3)	4.0 (0.7)	12.1 (3.0)	43(13)

TABLE II. *Mean (SD) values for fluoride in urine 24 h after exposure of rats to enflurane. Significant differences:* †$P < 0.05$ *compared with group given paracetamol and enflurane;* **$P < 0.01$ *compared with two groups not given enflurane*

Treatment	Volume of urine (ml)	Concentration of fluoride ($\mu g\ ml^{-1}$)	Total fluoride (μg)	Fluoride per body wt ($ng\ g^{-1}$)
Paracetamol	8.2 (0.7)	4.5 (1.8)	39.4 (17.3)	143 (54)
Paracetamol + enflurane	8.7 (3.0)	9.5 (3.7)**	79.0 (28.0)**	306 (66)**
Enflurane	8.4 (2.2)	17.0 (7.4)**†	133.1 (30.2)**†	470 (84)**†
None (controls)	8.1 (0.8)	4.3 (1.5)	40.3 (16.2)	139 (30)

the whole body were significantly greater in animals exposed to enflurane alone than in pretreated animals exposed to enflurane (table II).

The volume of urine did not differ for all four groups at 6 h (2.8 (0.6) ml) or 24 h (8.4 (2.0) ml).

At 24 h, the concentration of paracetamol and its metabolites (sulphate and glucuronide) in urine were similar for the group given paracetamol alone (17.5 (2.1) mg) and the group given enflurane in addition (16.9 (3.6) mg). These values represent 85% recovery of the doses given.

Paracetamol alone increased both AST (from 165 to 475 units ml^{-1}) and ALT (from 60 to 185

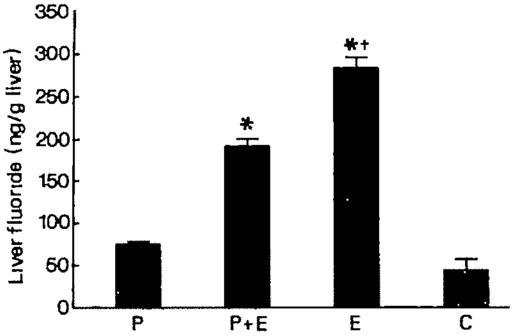

FIG. 2. Fluoride concentrations in liver samples 6 h after 16 rats were given paracetamol 7.5 mg/100 g body weight only (P); pretreatment with paracetamol and exposure to 1% enflurane (P+E); 1% enflurane only (E); or no treatment (controls) (C). Significant differences ($P < 0.05$): *compared with the two groups not given enflurane; †compared with animals pretreated with paracetamol and exposed to enflurane.

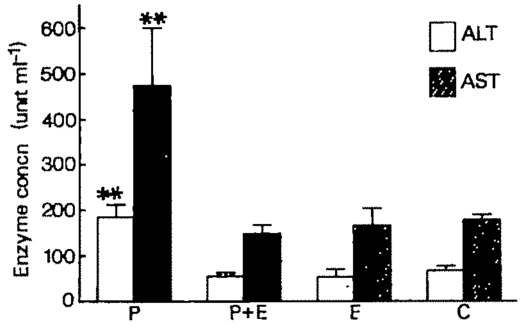

FIG. 3 Serum concentrations of the enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) after 16 rats were given paracetamol 7.5 mg/100 g body weight only (P); pretreatment with paracetamol and exposure to 1% enflurane (P+E); 1% enflurane only (E); or no treatment (controls) (C). ** Significant difference ($P < 0.01$) from all the other groups.

units ml^{-1}). The other two treatment groups and the control group had similar values for these two enzymes (fig. 3).

There were no pathological changes evident on histological examination of any liver sample.

DISCUSSION

Pretreatment with paracetamol appears to inhibit biotransformation of enflurane, as indicated by decreased concentrations of fluoride ion in serum, liver and urine. Although paracetamol is eliminated mainly by formation of the glucuronide and sulphate, a small and important portion is metabolized by the liver microsomal enzyme system, mainly cytochrome P_{450}, to form reactive metabolites [12]. Enflurane also is a substrate of the microsomal enzyme system of the liver. Inhibition of the biotransformation of enflurane by paracetamol may occur because of competition between the drugs for the microsomal enzyme system of the liver (possibly the enzyme system cytochrome P_{450}), or because of a toxic effect on the mixed function oxidase system.

Dehalogenation of enflurane was probably inhibited by paracetamol or its metabolites, as no changes occurred in urinary volume or in the concentration of paracetamol and its conjugates in urine, whereas fluoride output in urine was decreased by paracetamol at both 6 and 24 h, and serum fluoride decreased at 6 h, but not 24 h, after exposure of rats to enflurane. The decrease in serum and liver concentrations of fluoride after pretreatment with paracetamol further suggests that the difference in urinary concentrations of fluoride between treatment groups was a result, not of an effect on fluoride excretion, but of differences in the concentration of fluoride ion in serum; that is, enflurane underwent less metabolism in the liver when rats were pretreated with paracetamol.

For both groups given paracetamol there was no difference in its concentration in urine after incubation of urine samples with β-glucuronidase and sulphatase. This implies that enflurane had no effect on conjugation of the drug with glucoronate or sulphate.

The rats given paracetamol alone exhibited the greatest concentrations of AST and ALT. The group given the drug with enflurane exhibited AST and ALT concentrations similar to those of the control and enflurane-only groups. Enflurane may decrease reactive metabolities by altering the metabolic pathway of paracetamol or by creating competition between paracetamol and enflurane for the microsomal enzyme system of the liver.

Although no pathological changes were observed in any liver sample, the increases in the concentrations of AST and ALT in the group given paracetamol alone suggests subclinical liver damage.

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ANAESTHETIC MANAGEMENT FOR CAESAREAN SECTION IN A PATIENT WITH UNCORRECTED TRUNCUS ARTERIOSUS

N. C. T. WILTON, K. B. TRABER AND L. S. DESCHNER

SUMMARY

We describe the successful management of a 25-yr-old primigravida with uncorrected truncus arteriosus, requiring an urgent Caesarean section for delivery of a live infant and we discuss the rationale of using the chosen drug combination and the importance of adequate monitoring in selecting an anaesthetic technique based on the pathophysiology of the congenital cardiac lesion.

Truncus arteriosus is a rare congenital cardiac malformation in which only one artery arises from the heart. From this common vessel, the systemic, pulmonary and coronary arteries originate [1]. The prognosis for individuals with this lesion is poor. Untreated, the malformation is ultimately fatal, with most patients experiencing progressive congestive heart failure in infancy because of excessive pulmonary blood flow [2]. Occasionally, untreated patients do survive until adulthood, although their prognosis remains poor [3].

There has been only one previous case report of a patient with this lesion becoming pregnant, and although a live infant was delivered vaginally, the mother died early in the post partum period [4]. Information from a large review of patients with Eisenmenger's syndrome suggested that these patients have a high mortality rate associated with their pregnancy, and that this poor prognosis is worsened if Caesarean section is used to deliver a live infant [5].

We present the successful anaesthetic management of a patient with uncorrected truncus arteriosus who required Caesarean section for the delivery of a live infant.

CASE REPORT

A 25-yr-old woman (weight 77 kg) with a diagnosis of truncus arteriosus was referred to the High Risk Pregnancy clinic. The diagnosis of truncus arteriosus had been made provisionally at age 6 months when the patient developed congestive heart failure. No cyanosis was noted at this time (but increased pulmonary vascular markings were noted on chest x-ray). Cardiac catheterization at age 3 yr, undertaken because of decreasing exercise tolerance, confirmed the diagnosis of truncus arteriosus type III by the Collett and Edwards classification. Surgical intervention was refused because the family members were Jehovah's Witnesses and would not accept a blood transfusion. The patient was reviewed intermittently until age 17 yr and she remained clinically stable during that time. Repeated chest x-rays continued to show cardiomegaly with increased pulmonary vascularity, and ECG confirmed right ventricular hypertrophy. The patient was then lost to follow-up.

The patient was seen initially by us at 23 weeks gestation, but would not accept termination of pregnancy. Symptoms were mild exertional dyspnoea without evidence of orthopnoea, paroxysmal nocturnal dyspnoea, palpitations or oedema. The patient was admitted to hospital at 29 weeks gestation because of shortness of breath. No other change in her signs or symptoms had occurred.

Physical examination revealed heart rate 80 beat min^{-1} in sinus rhythm and arterial pressure 114/74 mm Hg. Heart sounds were normal S_1,

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TABLE I. *Haemodynamic and blood-gas data associated with general anaesthesia in a patient with uncorrected truncus arteriosus*

	Arterial pressure (mm Hg)	Heart rate (beat min^{-1})	CVP (mm Hg)	Oxygen saturation (%)	HCT (%)	pH	Pco$_2$ (kPa)	Po$_2$ (kPa)
Before intubation	100/60	100	3	80	49	7.39	5 1	7 8
After intubation	120/60	100	6	90	47	7 37	5.0	7.8
After delivery	100/60	70	6	87	45	7.40	4.6	8 3
After extubation	130/70	100	7	86	—	—	—	—
1 h after op.	140/70	80	3	87	44	7.36	5.0	6.8
6 h after op.	115/60	70	4	85	44	7.38	4 9	6 8
18 h after op.	120/60	75	6	83	46	7 42	4.7	6.2

single S$_2$ with an audible ejection click and 2/6 systolic ejection murmur. Central and peripheral cyanosis were present, as was clubbing of the fingernails. The haemoglobin concentration was 17.3 g dl^{-1} and the haematocrit was 52 %. Arterial blood-gas analysis showed a pH of 7.43, Pco$_2$ 4.2 kPa, Po$_2$ 6.3 kPa and oxygen saturation 83 % (Fi$_{O_2}$ 0.21). ECG showed heart rate 80 beat min^{-1}, PR interval 0.16 s, QRS interval 0.10 s with right ventricular hypertrophy. Echocardiogram confirmed truncus arteriosus with evidence of severe pulmonary artery hypertension by Doppler examination. Doppler studies also showed a 20-mm gradient across the truncal valve with mild truncal insufficiency. Ventricular function was normal. Therapy was commenced with digoxin 0.125 mg day^{-1} and heparin 7000 units s.c. twice daily. For the next 6 weeks, the patient remained in hospital and she received oxygen 2 litre min^{-1} via nasal cannulae, during which time she became slightly more dyspnoeic. Her haemoglobin oxygen saturation measured intermittently by pulse oximetry was 80–84 %. The patient's haemoglobin concentration remained between 15.0 and 17.3 g dl^{-1} and the haematocrit between 44 and 50 %. Repeated ECG showed no worsening of truncal insufficiency or ventricular function. During heparin therapy, a mild thombocytopenia (115–130 000) occurred, but the prothrombin time and activated partial thromboplastin time (PTT) remained within normal limits.

The fetus was monitored with a weekly non-stress test (NST), beginning at 30 weeks gestation. At 35 weeks gestation, the NST became non-reactive. An Oxytocin Challenge Test (used to assess the adequacy of fetal oxygenation), revealed deacellerations with poor short and long term variability. This suggested suboptimal oxygenation of the fetus [6] and it was decided, therefore, to proceed urgently with Caesarean section before the condition of the fetus deteriorated. Before Caesarean section, the haemoglobin was 16.8 g dl^{-1}, haematocrit was 51 % and oxygen saturation was 80 %. Ampicillin 2 mg and gentamycin 90 mg i.v. were administered to provide antibiotic prophylaxis.

We believed that the usual anaesthetic techniques for Caesarean section would not be appropriate. The patient was sedated with midazolam 7 mg i.v. A right internal jugular catheter was inserted for central venous pressure monitoring and a left radial arterial catheter was also inserted. Thirty millilitre of sodium citrate 0.3 mol litre^{-1} was administered by mouth. Following 3 min of preoxygenation, induction was performed using ketamine 2 mg kg^{-1}, fentanyl 5 µg kg^{-1} and suxamethonium 2 µg kg^{-1} with cricoid pressure. Following intubation, anaesthesia was maintained with 50 % nitrous oxide and 0.2–0.5 % halothane in oxygen to control arterial pressure. Vecuronium was given for neuromuscular blockade. Fifteen minutes after induction of anaesthesia and 2 min after uterine incision, a normal infant was delivered weighing 1.9 kg, with Apgar scores of 4 and 8 at 1 and 5 min, respectively. At the end of the operation an extradural catheter was inserted, and the residual neuromuscular block antagonized with glycopyrrolate 0.6 mg and neostigmine 2.5 mg i.v. Following extubation of the trachea, the patient was given 6 mg of preservative-free morphine in 10 ml of normal saline via the extradural catheter. Blood loss throughout the procedure was estimated at 0.6–0.8 litre and lactated Ringer's solution 2.2 litre was administered during the immediate preoperative and the intraoperative periods. Intraoperative and postoperative haemodynamic and blood-gas data are shown in table I.

An infusion of heparin was started 12 h after operation at a rate of 1000 unit h^{-1} and adjusted to maintain the PTT > 1.5 × control. Two units of packed red cells were required during the following 24 h to maintain an adequate haematocrit. The patient received two further extradural doses of morphine, at 18 h and 42 h after operation, and required minimal additional analgesia during this time.

Further recovery was uneventful until 6 days after operation when she developed left arm weakness lasting 3 min. This recurred on the 7th day after operation. Heparin i.v. was continued for a further 4 days, after which time therapy was changed to subcutaneous heparin. The mother was discharged on the 13th day after operation, receiving the following therapy: digoxin 0.125 mg twice daily, calcium gluconate 500 mg three times daily and heparin 10000 units s.c. three times daily. Nine months later, both mother and child were doing well.

DISCUSSION

This report describes the successful anaesthetic management of Caesarean section in a patient with truncus arteriosus. One other pregnancy has been described in a patient with this congenital heart lesion, but she died after giving birth to a live infant [4].

Truncus arteriosus represents a severe form of Eisenmenger's syndrome in that the pulmonary arteries are subject to systemic pressures and high blood flow from birth. Furthermore, as the output from both ventricles enters the common trunk, systemic blood tends to be desaturated and a compensatory polycythaemia develops from birth. From a review of Eisenmenger's syndrome and pregnancy, two important points become apparent: the maternal mortality with Caesarean section (75 %) was significantly higher than with vaginal delivery (34 %), and patients with a right ventricle exposed to systemic pressure from birth (ventricular septal defect) had a higher maternal mortality than those in whom right ventricular hypertension was likely to be a later phenomenon (atrial septum defect and patient ductus arteriosus) [5].

A survey of the world literature to date reveals 15 reported Caesarean sections in 14 patients with Eisenmenger's syndrome (secondary to various lesions), but none with truncus arteriosus. The overall mortality of these patients was 50 %. Of these reported cases, one patient received local anaesthesia only and died [7]. Two received lumbar extradural anaesthesia and survived [8, 9]. Seven received general anaesthesia [10–15] and only three of these survived. The method was not documented in the remaining five, although it is likely that they all received general anaesthesia [16–18].

The anaesthetic requirements and physiological changes in a pregnant patient with truncus arteriosus and Eisenmenger's syndrome undergoing general anaesthesia for Caesarean section differ from those of a normal pregnant patient. Anaesthesic techniques used during Caesarean section are designed to minimize cardiovascular and respiratory depression of the newborn, but marked changes in systemic and pulmonary vascular resistance may occur in the mother.

Oxygenation in a patient with truncus arteriosus depends on an adequate cardiac output and an appropriate balancing of blood flow through the pulmonary and systemic vasculature. Decrease in systemic vascular resistance (SVR) or increase in pulmonary vascular resistance (PVR) tends to decrease pulmonary blood flow, while opposite changes increase pulmonary blood flow. During pregnancy, particularly in the last trimester, the SVR normally decreases, as indicated by an increase in cardiac output despite a mild decrease in arterial pressure [18]. Haematocrit also tends to decrease, thereby further decreasing SVR. It is unlikely that these changes occurred in our patient as the haemocrit did not decrease and the oxygen saturation remained stable at 80–85 %, suggesting approximately balanced blood flow through the pulmonary and systemic circulation [19].

With Eisenmenger's syndrome it is not possible to decrease PVR by pharmacological means, therefore the anaesthetic management must be directed toward maintaining SVR and cardiac output while avoiding situations which increase PVR. The use of a Swan-Ganz catheter is not possible in this lesion. Continuous measurement of oxygen saturation by pulse oximetry, however, is particularly useful as it allows continuous assessment of the adequacy of pulmonary and systemic blood flow. Assuming that mixed venous oxygen saturation remains between 50 and 70 %, an oxygen saturation of 75–85 % represents approximately balanced systemic and pulmonary blood flows [20]. A decrease in oxygen saturation indicates inadequate pulmonary blood flow, whereas persistently increased oxygen saturation indicates an excessive pulmonary blood flow. If the cardiac output from the single ventricle cannot increase sufficiently, theoretically, systemic hypotension and acidosis may develop. End-tidal carbon monitoring would also be helpful in this type of patient, in addition to intermittent measurement of arterial $P\text{CO}_2$ by blood sampling, as the pulmonary vascular resistance is sensitive to pH changes, particularly in the presence of hypoxia [21].

Ketamine was used as an induction agent as it produces minimal changes in PVR and does not adversely affect the relative blood flows through the pulmonary and systemic circulation [22, 23]. Fentanyl was used in an attempt to obviate increases in PVR associated with tracheal intubation and surgical incision [24]. Although a dose of only 5 μg kg^{-1} was used, no decrease in systemic oxygenation occurred, suggesting that marked changes in PVR did not occur. Nitrous oxide has been found either to increase [25], or not to affect PVR [26]; in our patient no adverse effects were observed as assessed by oxygen saturation. Low concentrations of halothane were used to ensure amnesia for the procedure, and this did not produce untoward haemodynamic changes.

Although extradural anaesthesia has been used successfully in patients with Eisenmenger's syndrome, both cases reported were elective, and this allowed gradual onset of analgesia and accompanying sympathetic block [8, 9]. The main concern with the use of extradural anaesthesia for Caesarean section is that the decrease in systemic vascular resistancce that occurs in the presence of a fixed, increased pulmonary vascular resistance may lead to a decrease in pulmonary blood flow with worsening of cyanosis. However, general anaesthesia allows independent manipulation of the pulmonary and systemic circulations by appropriate physiological and pharmacological means. Pulmonary hypertension and increases in pulmonary vascular resistance (in particular) are not amenable to treatment by extradural analgesia, but may respond to hyperventilation and high dose opioids.

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COMPARISON OF PULSE OXIMETERS: EFFECTS OF VASOCONSTRICTION AND VENOUS ENGORGEMENT

C. J. WILKINS, M. MOORES AND C. D. HANNING

SUMMARY

The effects of cold-induced vasoconstriction and venous occlusion on the detection of induced hypoxaemia by four pulse oximeters were examined in 10 volunteers. In three further subjects vasoconstriction was maintained until at least one instrument failed to detect the induced hypoxaemia. Time taken to detect hypoxaemia was increased for all instruments to between two and three times the instrument's own control value for both vasoconstriction and venous engorgement ($P < 0.01$*). There was highly significant variation in detected minimum saturation between the instruments (*$P < 0.001$*). One instrument failed to detect the full extent of desaturation under the experimental conditions and was more likely to fail completely to detect desaturation than the other test instruments when influenced by vasoconstriction (*$P < 0.05$*). Significant impairment in the performance of all the instruments tested occurred in the presence of normal pulse signals. The duration of detected reductions in oxygen saturation was not significantly affected.*

Pulse oximetry is an emerging standard in clinical monitoring [1]. Since the first description of the technique [2], many instruments have been introduced commercially. All work on the principle of absorption spectroscopy, but there are differences in probe design and sampling frequency, and in the constants and algorithms used to process the data [3]. These differences may affect instrument performance.

Pulse oximetry relies upon the presence of a pulsating vascular bed. It is likely that signal detection would be impaired in the presence of vasoconstriction or venous congestion, conditions which may occur readily in clinical practice. Previous evaluations of pulse oximeters [3–8] have not specifically examined this problem.

The aim of this study was to evaluate five commercially available pulse oximeters as clinical monitors of oxygenation in the presence of these factors.

SUBJECTS AND METHODS

Ethics Committee approval was obtained and all subjects gave informed consent to be included in the study, which was performed in two parts.

Part I

The instruments tested in this part were the Ohmeda 3700, the Novametrix 500 (Novametrix Medical Systems Inc.), the Criticare Systems Inc. 501, and the Accusat (Datascope Corporation). Ten healthy volunteers (eight male) aged 25–40 (mean 29) yr took part. All had satisfactory tests of ulnar collateral blood flow. Subjects rested comfortably on a couch and standard finger probes from the test instruments were applied in random order to the fingers of one hand; the thumb was not used. Cards marked with each of the 24 possible combinations of probes and fingers were placed in unmarked envelopes and one drawn for each subject (thus not all combinations were used). A Biox III (Ohmeda) applied to the subject's ear was used for safety purposes and to ensure uniformity of Sa_{O_2} changes between periods of low oxygen breathing. The outputs of the instruments were fed to a chart recorder calibrated according to the manufacturer's instructions.

This article is accompanied by Editorial II.

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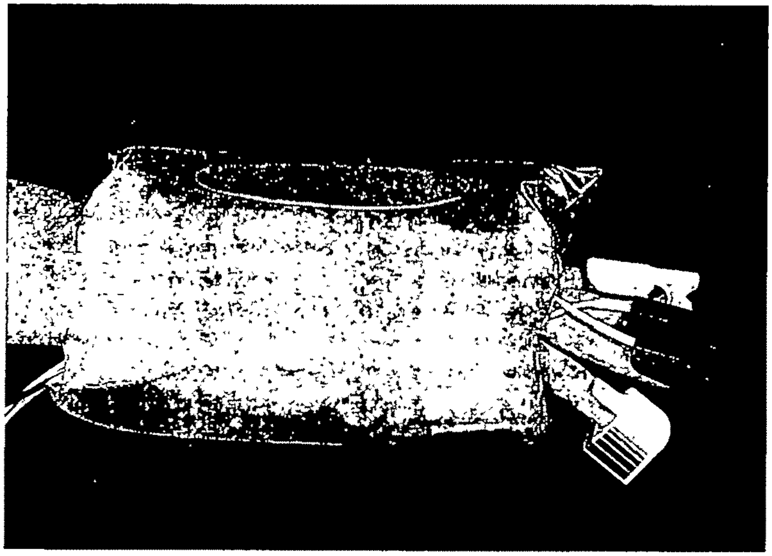

FIG. 1. Surface cooling technique and finger probe placement.

Control readings

Two episodes of hypoxaemia were induced by the inhalation of 10% oxygen in nitrogen from pre-filled Douglas bags, via a closely fitting non-rebreathing mask after a 5-min period for baseline observations. Each episode lasted 2 min, but was terminated if the Biox III indicated that arterial oxygen saturation (Sa_{O_2}) had decreased to 79% or less. Subjects breathed room air for 3 min between episodes of hypoxaemia.

Venous congestion

A standard sphygmomanometer cuff applied to the upper arm was inflated to 40 mm Hg to induce venous congestion. After 5 min, two further episodes of hypoxaemia were induced as before.

Vasoconstriction

The subject's forearm was placed into a water-filled plastic envelope cooled overnight in a domestic refrigerator (fig. 1). The oximeter probes were allowed to protrude from the envelope to avoid their direct cooling. After 5 min, two further episodes of hypoxaemia were induced as before.

The nature of any alarm or warning signal from the instruments was noted at all stages of the experiment and was acted upon as appropriate.

Analysis of data

The second of the two hypoxaemic episodes for each of the three experimental conditions (control, venous congestion and vasoconstriction) was analysed. Data for minimum Sa_{O_2}, detection time (time from start of breathing 10% oxygen to the first downward deflection on the Sa_{O_2} trace) and duration of the reduction in Sa_{O_2} to less than resting values were obtained from the permanent record.

No assumptions were made regarding the distribution of the data, and all statistical tests used were for non-parametric data. Data from the Biox III (ear probe) were not included in the analysis because it was not the purpose of the study to compare the performance of ear and finger probes.

For each of the categories of data, the variation between the three sets of experimental conditions and between the four test instruments was analysed by the Kruskal–Wallis one-way analysis of variance using Oxstat. Wilcoxon signed rank tests were used to test for differences between the experimental conditions for each instrument. It was possible to use a test for paired data because each instrument acted as its own control within each subject. Differences between instruments were examined using the same test, but the results of these are reported only where the performance of one instrument was significantly different from that of all the others.

Part II

The instruments tested in this part were the same as those used in part I, except that the Lifestat 1600 (Physio-control Corporation) was substituted for the Criticare Systems Inc. 501 (CSI). A Biox III with ear probe was again used for safety purposes. Three subjects were studied, each on four separate occasions, and finger probes from the test instruments were applied to a different finger for each experimental session. Thus each of the probes was tested on each finger of each subject.

As before, hypoxaemia was induced by the inhalation of 10% oxygen in nitrogen for periods of 2 min separated by 3-min intervals. After two such episodes, the cold envelope was applied as before. The sequence of hypoxaemic episodes was continued for 1 h or until all the instruments failed, whichever was the shorter period. Failure was defined as an inability to detect a reduction in Sa_{O_2} of greater than 5% from resting values. As before, any indicated alarm was recorded and acted upon as appropriate.

Analysis of data

The number of instrument failures was recorded for each instrument and the data analysed by a Chi-squared test with Yates' correction for small numbers.

RESULTS

Part I

All instruments detected a decrease in Sa_{O_2} for all episodes of hypoxaemia and continued to display normal pulse signals throughout the experiment. There were no significant differences between instruments in resting Sa_{O_2} or in minimum Sa_{O_2} between experimental conditions (as indicated by the Biox III).

Detection time (table I)

Analysis of variance revealed highly significant differences between the three sets of experimental conditions ($P < 0.001$).

Control conditions. There were no important differences between the test instruments.

Venous congestion. The mean detection time of all the test instruments was increased significantly to between two and three times each instrument's own control value ($P < 0.01$) (table I). In the most extreme case, detection time was increased from a control value of 120 s to 405 s.

Vasoconstriction. The mean detection time of all the instruments was increased significantly, usually to between two and three times the instrument's control value ($P < 0.01$). In one case the detection time was increased from a control value of 95 s to 275 s.

There were no significant differences in detection times amongst the test instruments for both vasoconstriction and venous congestion.

TABLE I. *Detection time (s) for induced hypoxaemia for each instrument for the three experimental conditions (mean (range)).* n = *10.* **$P < 0.01$; ***$P < 0.001$ *for comparisons with own control (Wilcoxon signed rank test)*

Instrument	Control	Venous congestion	Vasoconstriction
Biox III	28.3 (19–35)	28.5 (24–30)	30.5 (20–35)
Ohmeda 3700	58.4 (14–120)	159.7 (48–405)**	120.3 (53–225)***
C.S.I.	66.3 (14–130)	152.5 (35–300)**	140.6 (40–290)***
Novametrix	57.3 (14–95)	122.0 (35–155)***	121.1 (67–275)**
Accusat	52 9 (10–90)	129.5 (30–230)***	95.2 (42–210)***

TABLE II. *Minimum* Sa_{O_2} *(%) during breathing 10% oxygen for each set of experimental conditions (mean (range)).* n = *10.* *$P < 0.05$ *for comparison with own control (Wilcoxon signed rank test)*

Instrument	Control	Venous congestion	Vasoconstriction
Biox III	83.0 (79–86)	81.4 (79–85)	81.1 (79–84)
Ohmeda 3700	78.9 (72–82)	82.9 (74–91)	77.9 (72–83)
C.S.I.	81.6 (72–84)	85.0 (79–95)*	80.9 (77–84)*
Novametrix	82.6 (78–88)	86 4 (82–90)*	87.8 (80–96)*
Accusat	82.7 (78–85)	83.9 (78–89)	83.1 (78–89)

TABLE III. *Number of instrument failures and warnings of failure for each set of experimental conditions in part II.* *$P < 0.05$ *for comparison with Ohmeda 3700 (Chi-squared test)*

Instrument	Control	Vasoconstriction	Warning given
Ohmeda 3700	0	0	—
Accusat	0	4	4
Lifestat 1600	0	1	1
Novametrix 500	0	8*	2

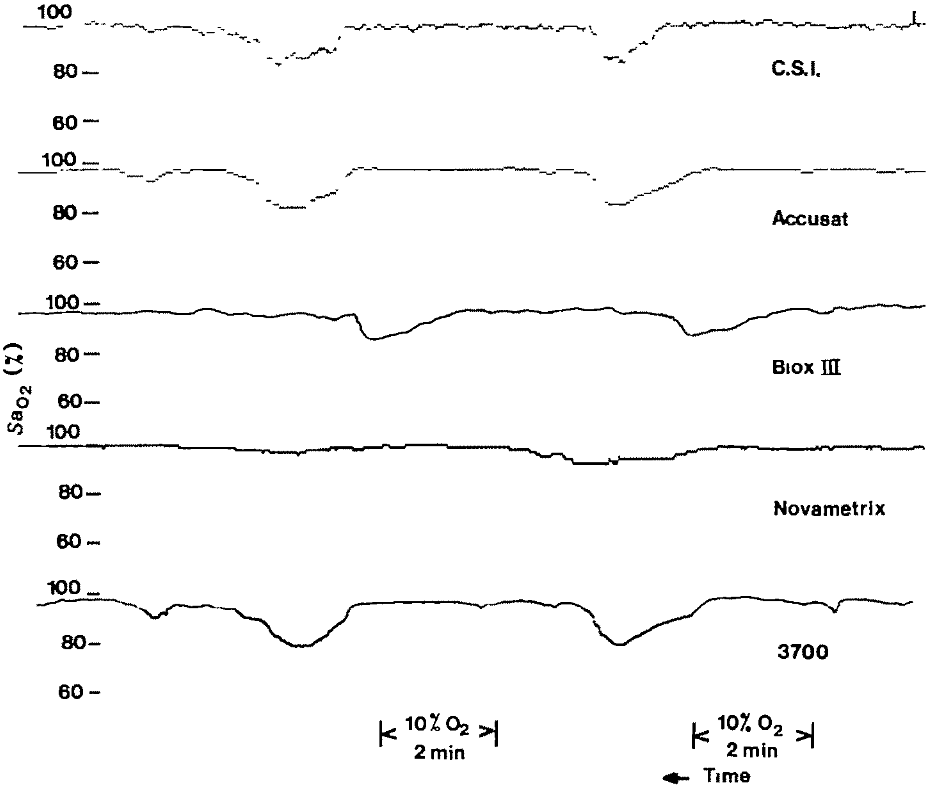

FIG. 2. The effect of vasoconstriction (two consecutive episodes of hypoxaemia). Note delay in response and failure of Novametrix 500.

Minimum Sa_{O_2} (table II)

There were no significant differences between the three sets of experimental conditions, but there was marked variability between the test instruments ($P < 0.001$).

Control. The minimum Sa_{O_2} was significantly less for the Ohmeda 3700 than for all the other instruments ($P < 0.05$). There were no other differences between the instruments (table II).

Venous congestion. The minimum Sa_{O_2} for the Novametrix 500 was significantly greater than its own control value ($P < 0.05$).

Vasoconstriction. The minimum Sa_{O_2} for the Novametrix 500 was significantly greater than its own control value ($P < 0.01$). The value of the Ohmeda 3700 was significantly less than those of all the other instruments ($P < 0.05$).

Duration of detection reduction in Sa_{O_2}

There were no significant differences between instruments or between experimental conditions.

Part II

There were 12 separate experimental sessions and the maximum number of possible failures for each instrument was therefore 12 (table III).

An example of instrument failure is seen in figure 2. Because the numbers are small, only the figures for the Biox 3700 and the Novametrix 500 were subjected to statistical analysis by chi-squared test (with Yates' modification for small numbers). The difference was significant at $P < 0.05$.

DISCUSSION

Analysis of the performance of pulse oximeters is complex. We identified three elements which we thought likely to be affected by a reduction in limb perfusion, namely detection time, duration of desatuation and minimum Sa_{O_2}. Other authors [3, 8] have been concerned with the absolute accuracy of pulse oximeters and have measured Sa_{O_2} directly to provide the standard. The purpose of the present study was to examine the influence of venous congestion and vasoconstriction on the performance of the test instruments, rather than to determine their absolute performance, and we have no data for absolute Sa_{O_2} or Pa_{O_2}. We used an oximeter (Biox III) applied to the subject's ear to ensure uniformity of desaturation between hypoxic tests (not as a measure of true Sa_{O_2}) and have made comparisons for each instrument under the influence of venous congestion and vasoconstriction with its own control value.

Uniformity in the degree of desaturation was achieved, there being no differences in minimum Sa_{O_2} for the three sets of conditions. It is not possible to state which of the instruments was reflecting the true Sa_{O_2} most accurately, and thus the meaning of comparisons of Sa_{O_2} between instruments would be questionable. We have, therefore, not made such comparisons, but have commented only on the variability amongst the group of instruments, except where one instrument was different from all of the others.

Vasoconstriction occurs commonly in patients undergoing surgery and intensive care and may be caused by cold, hypovolaemia, drugs, inadequate anaesthesia or other factors. We have attempted to mimic these conditions in the laboratory by using a surface cooling technique. The degree of vasoconstriction produced was not quantified, but all subjects found the cold stimulus unpleasant or even painful and all displayed marked digital pallor. The oximeter probes protruded from the envelope and were not subjected to direct cooling, although some indirect cooling must have occurred. None of the probes tested incorporates a heating element. This model may not exactly represent the conditions found in clinical practice, particularly if there are concomitant changes in cardiac output, but it was simple and non-invasive.

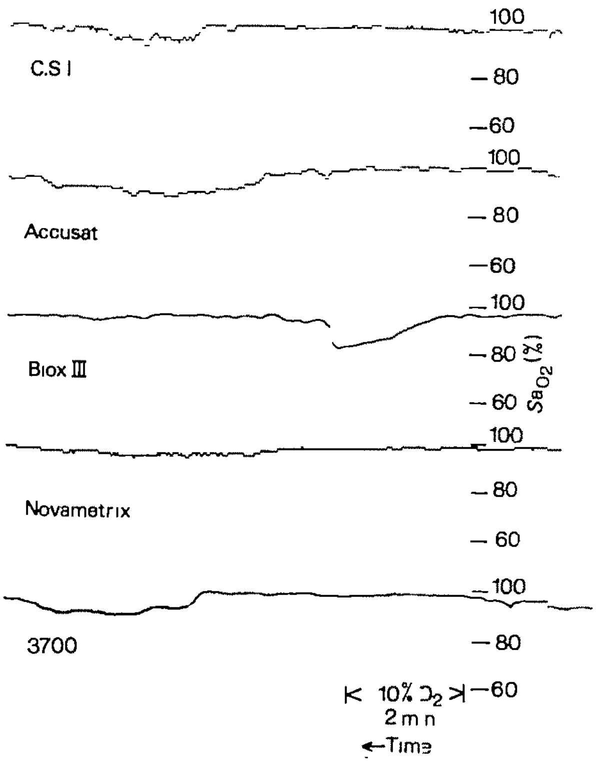

FIG. 3. The effect of venous congestion. All the instruments show marked delay in detecting desaturation and there is almost complete failure of the Novametrix 500.

Venous congestion may be produced by awkward positioning of the patient, by venous pooling caused by gravity or by increased central venous pressure. It may not always be obvious to the anaesthetist if the affected part is obscured by surgical drapes.

This study demonstrated the significant effect of vasoconstriction and venous congestion on the performance of pulse oximeters.

Detection time was increased consistently (figs 2 and 3). A mean delay of 150 s in detecting a hypoxic insult is clearly undesirable. The most extreme delay was 405 s. These delays occurred at a time when the instruments were displaying normal pulse signals.

The increase in detection time probably has two components. The principal component, the reduced blood flow to the fingers, is physiological. The second is related to the algorithm of the instrument: the displayed value of Sa_{O_2} is derived from many discrete values which are weighted according to their quality and then averaged. A reduced pulse volume may influence the weighting placed on each discrete measurement of Sa_{O_2} and thus on the displayed value. It is interesting that the Novametrix 500 continues to display a value for Sa_{O_2} even if only one valid pulse (peak–trough pair) has been detected during the previous 25 s, and this may explain its sensitivity to reduced perfusion. This information was not available for the other instruments.

Most of the instruments gave similar values of minimum Sa_{O_2} for the three conditions (control, venous congestion and vasoconstriction). This is in keeping with previous work [9] in which one instrument gave reliable data in spite of the infusion of vasopressor drugs. However, one instrument (the Novametrix 500) failed to detect the maximum extent of the reductions in Sa_{O_2} when influenced by venous congestion or vasoconstriction. This tendency was confirmed in part II of the study, when the same instrument failed more often than any of the others. The same instrument has been shown by others to possess marked variability in performance [8]. More disturbingly, this instrument gave no alarm signal on six of the eight occasions when it failed. The Accusat and Lifestat 1600 both gave clear warning of poor quality signals when they failed. The incidence of instrument failure did not appear to be influenced by site of probe placement.

It is possible that an individual instrument may perform badly because it is faulty or because of sampling error in the face of variation between instruments. It has been reported that two instruments of the same type gave widely differing Sa_{O_2} values when connected to the same patient [10]. It is impossible for the user to know that an instrument is inaccurate, because no form of calibration is required.

New versions of several of the instruments tested (including the Novametrix 500) were introduced after we began the study and may possess different performance characteristics.

We conclude that:

(1) Venous congestion and cold-induced vasoconstriction considerably increased the detection time for induced hypoxaemia.

(2) The presence of a normal pulse signal does not always imply that perfusion is adequate for the rapid detection of hypoxaemia.

(3) There may be important differences between instruments in their susceptibility to vasoconstriction and venous congestion.

(4) There was marked variation between instruments in the minimum saturation detected.

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A NEW MICROPROCESSOR-CONTROLLED ANAESTHETIC MACHINE

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SUMMARY

This paper describes the development of a microprocessor controlled anaesthetic machine comprising an integrated anaesthetic apparatus and monitoring system. Following prolonged reliability trials in the laboratory, changes have been made to major components which were described in earlier publications.

Most of the anaesthetic apparatus which is in current use is simple, robust and mechanically reliable. Versatility is achieved by the use of interchangeable vaporizers, breathing systems and ventilators, but this leads to several problems. First, the add-on units may be produced by different manufacturers, so there is no guaranteed compatibility between components. Second, there may be no interaction between the different components; for example, it may be possible to switch on a ventilator when there is no flow of fresh gas into the system. Third, breathing systems have to be constructed from a number of separate components, so that misconnections may result. Thus versatility is gained at the expense of patient safety. Furthermore, the machine with many add-on components is usually ergonomically unsound. Although the mortality and morbidity attributable directly to anaesthetic apparatus is relatively low [1–5], there are undoubtedly a number of near-misses which are not reported. Many other minor faults are detected regularly by anaesthetists and remedied without risk to the patient [6].

In recent years there has been an increased use of devices which monitor machine function, but care is needed to ensure that the monitoring system can detect all possible hazard situations. This is achieved best by designing an integrated anaesthetic apparatus and monitoring system.

Many monitoring devices use microprocessor technology for control and artefact rejection. It is therefore a natural progression to utilize microprocessors to control the components of an anaesthetic machine and produce an integrated monitoring system. The present paper describes the development of a microprocessor-controlled anaesthetic machine based on these principles.

TECHNOLOGY

We have made full use of the power of microprocessor control to simplify the mechanical components of the machine. For example, it would be uneconomical and unnecessarily complex (and, therefore, less reliable) to take an existing anaesthetic vaporizer which incorporates elaborate mechanical and pneumatic devices to compensate for the effects of flow, pressure and temperature variations on the delivered concentration, and then to drive the control knob by an electric motor under microprocessor control. However, if the microprocessor is used to control the addition of vapour to the fresh gas flow, the vaporizer may be reduced to a very simple mechanical device.

Microprocessors are composed fundamentally of on/off switches and so are interfaced more easily to digital rather than analogue devices. For example, the flowmeter control valves of the

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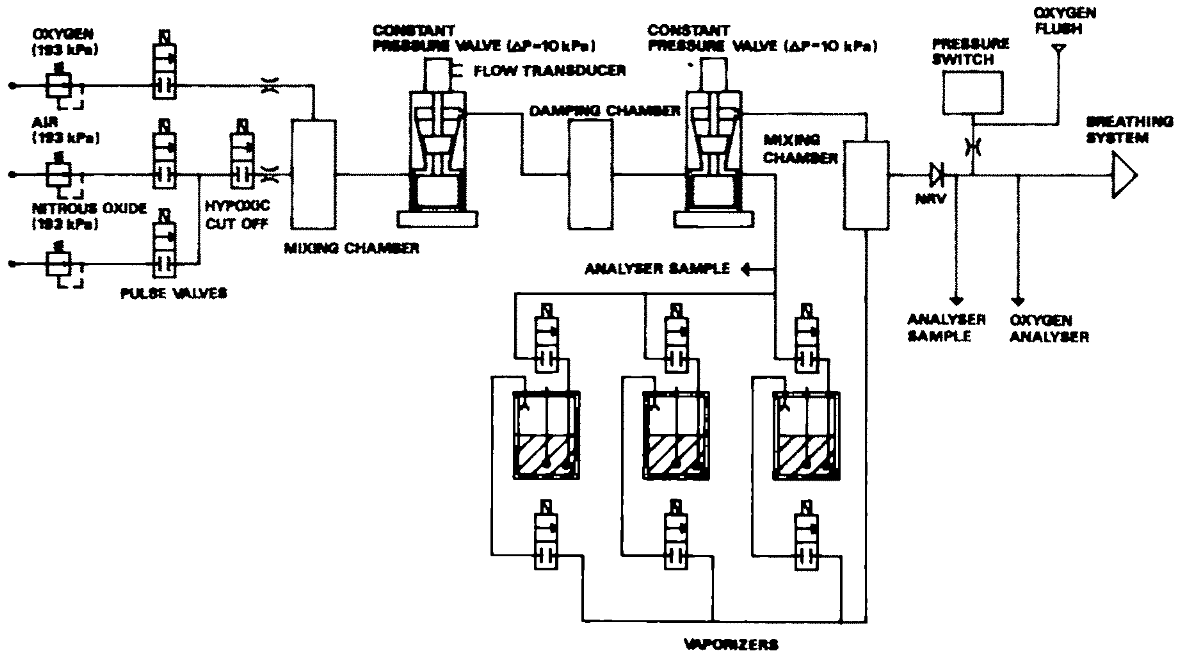

FIG. 1. Mechanical components of fresh gas and vaporizer units.

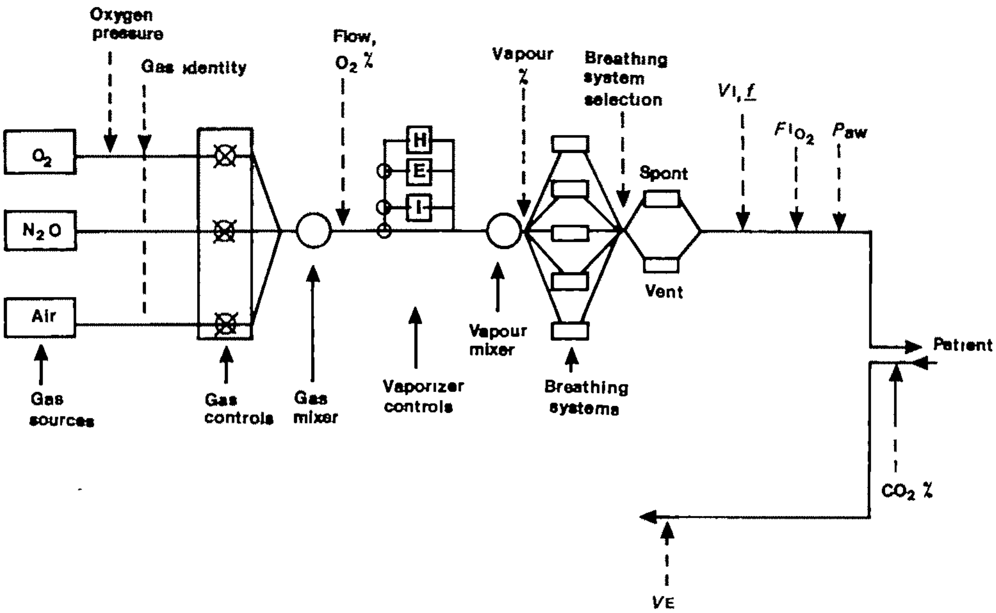

FIG. 2. Relationships between controls (solid arrows) and monitoring of machine function (dotted arrows) on microprocessor-controlled anaesthetic machine. V_I and V_E = inspired and expired volumes; f = frequency; Paw = airway pressure; $F_{I_{O_2}}$ = inspired oxygen concentration; CO_2 % = carbon dioxide concentration; O_2 % = oxygen concentration.

conventional machine are analogue devices which have been replaced in the new design by a digital system which generates small, fixed volumes of gas, the number of pulses of gas being adjusted to produce the desired flow. The concentrations of the gases can be controlled by the ratio of flows through two such devices [7] and, in a similar manner, vapour can be added in the form of small volume pulses of saturated vapour from a copper kettle type of vaporizer [8].

Figure 1 shows the arrangement of the mechanical components of the new machine and figure 2 shows how the integrated monitoring system checks continuously each aspect of machine function. The fresh gas supplies are connected to regulators to produce constant low-pressure sources which feed the solenoid-operated gas control valves. The pulses of gas passing through these valves in the open position are discharged through sonic chokes into a mixing chamber which is maintained at a constant pressure by a variable orifice–constant pressure valve. This acts also as a flowmeter by measuring the displacement of the float as in a Rotameter. A second constant pressure valve provides a pressure differential to control similar pulsed gas flow into the vaporizer units. The vaporizers are designed to ensure that the gas pulses passing through the vaporizer are fully saturated with vapour. As the temperature within the vaporizer is measured and the vapour pressure curve is known, it is possible to predict the flow of gas through the vaporizer which is required to produce a known concentration in the final gas mixture.

Gas and vapour analysis in the fresh gas system is performed by an interferometer [9]. The oxygen concentration in the inspired limb of the breathing system is measured by a separate paramagnetic analyser, which is used also to measure the fresh gas oxygen concentration when oxygen/air is selected. There is a separate infrared carbon dioxide analyser which continuously analyses the gas sample from the patient Y-piece or tracheal tube. Inspired and expired gas volumes are measured by turbine flowmeters in the inspiratory and expiratory limbs of the breathing system. Airway pressure is sensed by a pressure transducer close to the inspiratory valve and also by an aneroid gauge connected directly to the breathing system.

It will be apparent that each machine function is provided with a checking device which monitors its function. However, these devices are not used to produce closed-loop control. Each function is programmed and controlled by a microprocesor according to the setting of a manual control, whilst the output of the checking device is displayed on the control panel by a separate microprocessor so that the operator can compare visually the set and measured values. In addition, the microprocessors compare continuously the set and measured values and alert the operator if a significant discrepancy occurs, or if any other hazard situation arises.

DESIGN SPECIFICATION

The machine consists of a base unit, a control/display panel, and a shelf for patient monitoring equipment (fig. 3). The base unit contains the gas supplies, and the gas mixing, vaporizing, gas analysis, breathing system and ventilator modules, together with space for a drawer or suction unit.

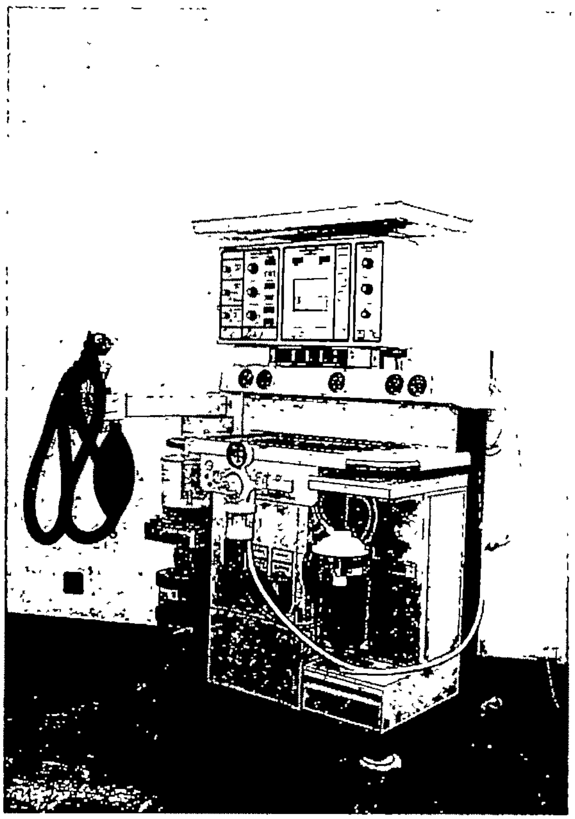

FIG. 3. General view of the machine with ventilator-breathing system module on the left, vaporizer filling ports in the middle and a suction unit on the right. Cylinders are mounted on the back of the machine.

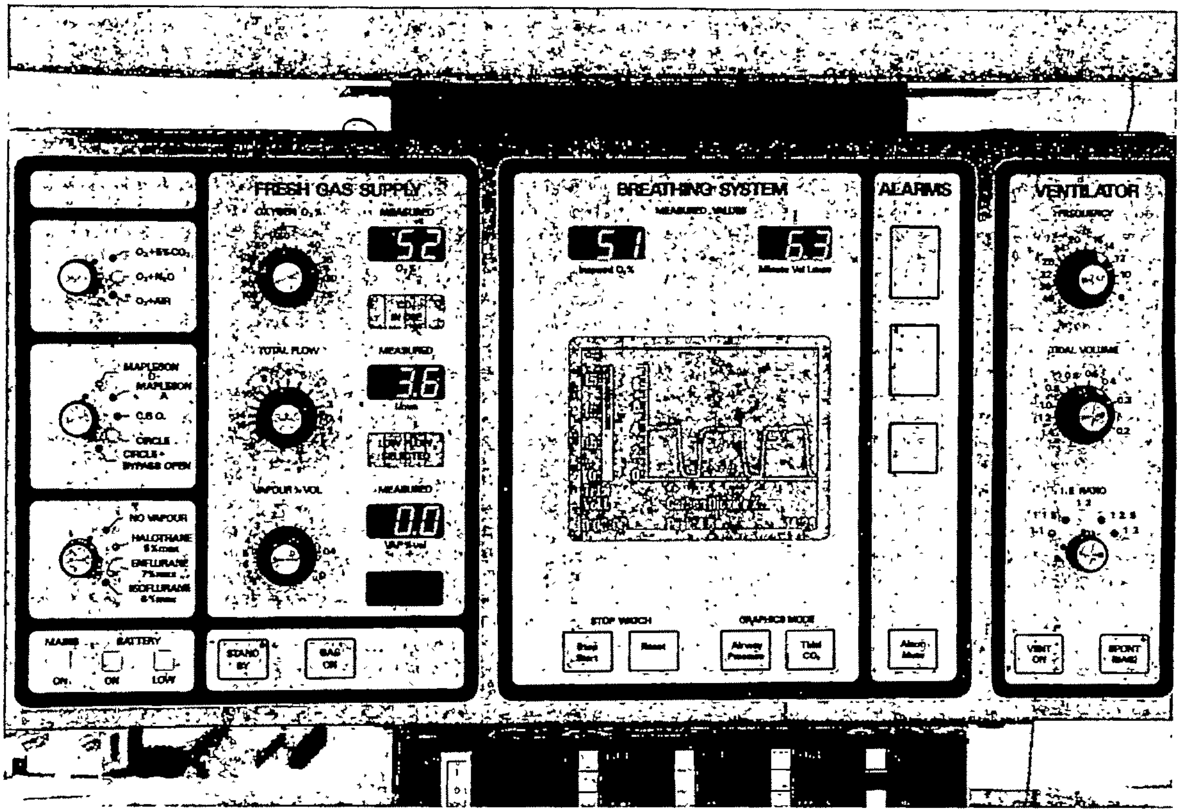

FIG. 4. The control panel showing the fresh gas, breathing system and vapour selector controls on the left, with the controls and measured values of oxygen concentration, flow and vapour concentration immediately to the right. The ventilator controls are on the extreme right of the panel, whilst the centre panel contains the breathing system monitors and alarms. An analogue trace of airway pressure or carbon dioxide concentration may be selected for display on the electro-luminescent panel, a vertical bargraph of tidal volume always being displayed on the left of this panel The stop-watch and digital clock displays are situated in the two lower corners.

The cylinder contents and pipeline supply gauges are situated at the back of the machine above the worktop, and the mains switch and illuminated bargraphs, showing which vaporizer is in use and its state of filling, are incorporated in a small panel above the pressure gauges. The controls and displays are situated on a panel which can be moved sidways and rotated so that it lies over the breathing system module at an angle of 45° to the long axis of the base unit. This brings the displays close to the head of the patient, but does not impair the anaesthetist's view of the operation.

The control/display panel is divided into three main sections (fig. 4). The left-hand section contains the controls for selection of fresh gas mixture, breathing system and vapour, together with the controls for oxygen concentration, fresh gas flow and vapour concentration. The measured values for fresh gas oxygen concentration, flow and vapour concentration are displayed digitally to the right of the controls. The ventilator controls are situated on the right hand section of the panel, whilst the centre panel contains the breathing system monitors and alarms. In the centre of this section there is an electro-luminescent (E-L) screen which displays information on tidal volume as a vertical bargraph, and breathing system airway pressure or carbon dioxide concentration, in analogue and digital form, together with malfunction messages in English text. The time of day and output from the stop-watch are also displayed (fig. 5). The inspired oxygen in the

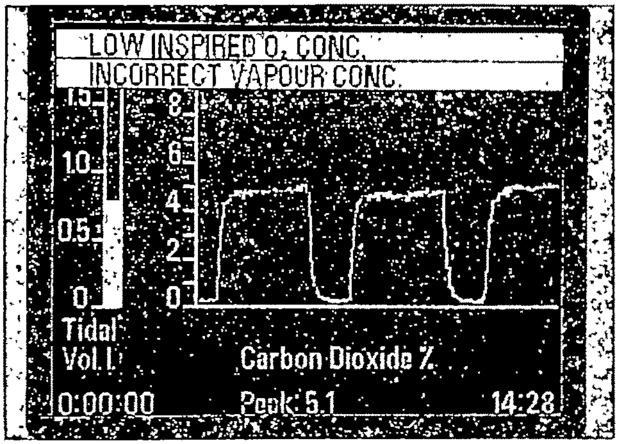
LOW INSPIRED O₂ CONC.
INCORRECT VAPOUR CONC.

FIG. 5. Electro-luminescent panel showing text messages (black letters on white background) with analogue displays (white on black background). The digital display of peak end-tidal carbon dioxide or airway pressure now shows the variable not chosen for analogue display, so that both variables can be monitored continuously.

breathing system and the expired minute volume are displayed digitally above the E-L screen, and there are stop-watch controls and switches for selection of the graphics mode below the screen.

Control functions

Fresh gas supply. The machine provides mixtures of oxygen–air or oxygen–nitrous oxide in the range 25–100 % v/v oxygen at total gas flow rates varying from 2 to 20 litre min^{-1}. An oxygen–5 % v/v carbon dioxide gas mixture may also be selected. The gas mixture selected is shown by an indicator light adjacent to the selector switch and a yellow warning panel is illuminated when oxygen–5 % v/v carbon dioxide is selected. Gas flow is initiated by pressing the "Gas On" button, and terminated by pressing "Standby". Subsequent depression of the Gas On button reactivates the set fresh gas flow and oxygen concentration, but vapour addition is not recommenced automatically. If the vapour control has not been zeroed, a "reset to zero" reminder is illuminated and must be obeyed before a selected vapour concentration is delivered.

Vapour concentration. Halothane 0–5 % v/v, 0–7 % v/v enflurane or 0–6 % v/v isoflurane may be added to the respired gases, selection of the correct vapour being confirmed by an indicator light situated by the vapour selector control, and by the illumination of the appropriate vaporizer filling indicator on the lower panel.

The breathing system module. The machine has a 22/15-mm inspiratory port or common gas outlet and a 22-mm expiratory port. Actuation of a selector switch on the control module permits a choice of one of the following breathing systems (fig. 6): (a) common gas outlet (for connection of an oxygen mask, paediatric breathing system, etc.); (b) Mapleson A (Magill/Lack) [10]; (c) Mapleson D (Bain) [11]; (d) circle with carbon dioxide absorption; (e) circle with gas bypassing the absorber. A non-rebreathing system can be provided also by small modifications to the microprocessor programme and the valve block in the breathing system module.

Positive identification of the breathing system in use is shown by an indicator light on the breathing system selection control. All breathing systems except (a) utilize two 1-m × 22-mm corrugated tubes to connect the inspiratory port and expiratory port to the patient connection port. If expired gas is detected by the expiratory flow meter when "Common Gas Outlet" is selected, a "check breathing system" warning is displayed on the E-L screen.

With Mapleson A, D or circle breathing systems, ventilation may be either spontaneous or controlled manually, the APL (adjustable pressure limiting) valve being spring-loaded as in conventional systems, but controlled remotely from a knob situated close to the bag mount. This arrangement allows the volume of gas spilt from the breathing system to be adjusted smoothly during manual ventilation, and also allows the APL valve to be used as a PEEP valve during mechanical ventilation. The ventilator is activated by a push-button control on the ventilator panel, but functions only when the Gas On button has been pressed and when the Mapleson D or circle systems have been selected. This prevents accidental use of the ventilator when there is no fresh gas flow, or when the breathing system selector control has been switched to Common Gas Outlet or Mapleson A [12].

Mechanical ventilator. This is a time-cycled flow-generator which compresses a rising bellows. The ventilator has a frequency range of 8–40 b.p.m., a tidal volume range of 200–1500 ml and a minute volume range of 3–16 litre min^{-1}. The inspiratory:expiratory time ratio is variable in

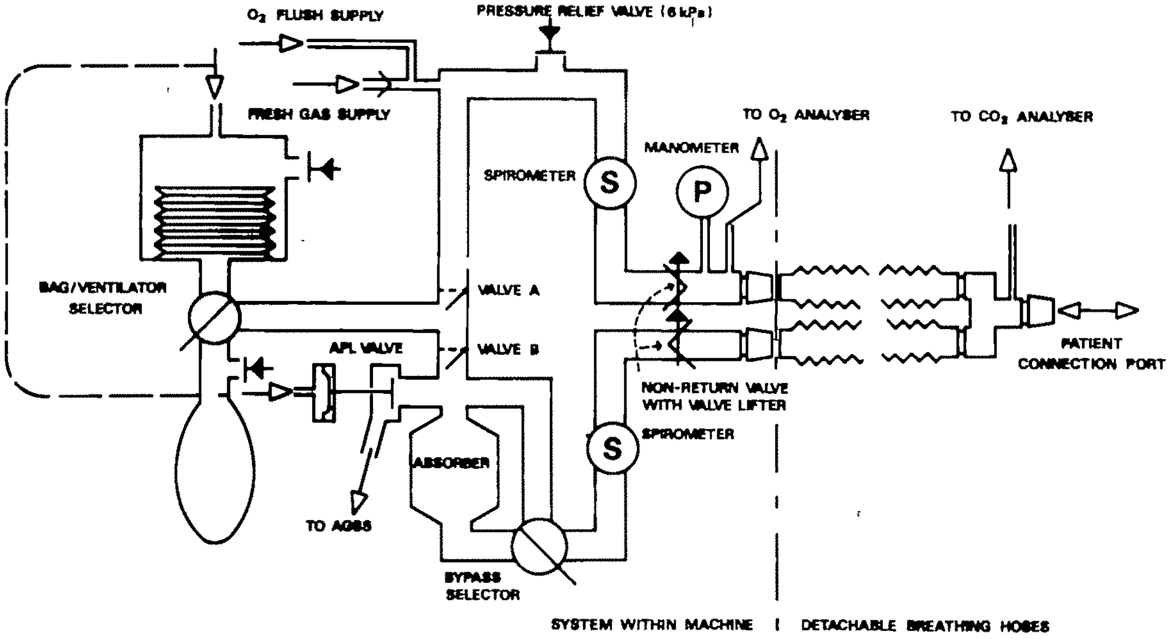

FIG 6. Breathing system showing position of bi-directional flow meters (S) and valves controlling direction of gas flow. When valves A and B are open a circle system is produced. A non-rebreathing system may be created by closing valves A and B and bypassing the absorber. In both these systems the non-return valves near to the patient connection ports are active. When the latter valves are inactivated so that gas can flow in both directions, a Mapleson A system can be formed by opening valve A and closing valve B, whilst a Mapleson D system is formed by opening valve B and closing valve A. The adjustable pressure limiting (APL) valve enables excess gas to be spilt from the system and also acts as a PEEP valve during controlled ventilation. AGSS = anaesthetic gas scavenging system.

fixed steps between 1:1 and 1:3. The microprocessor alters the stroke volume of the bellows to compensate for changes in fresh gas flow, so that a constant tidal volume is maintained with different fresh gas flows or breathing systems. There is an end-inspiratory pause so that changes in dynamic compliance and airway resistance may be deduced from the analogue airway pressure display and expired volume measurement.

Monitoring of machine function and alarms

A Ritchie whistle provides an audible warning of a reduction in pressure in the oxygen line leading to the gas mixing unit. Fresh gas oxygen concentration, total fresh gas flow and vapour concentration are displayed by large LED digital displays close to the appropriate control (fig. 4). Deviation of the measured value of oxygen concentration, fresh gas flow rate or vapour concentration from the set value by more than the predetermined tolerance is indicated by flashing of the relevant digital display (table I). Breathing system inspired oxygen concentration (monitored by the paramagnetic analyser in the breathing system inspiratory limb) and expired minute volume are displayed at the top of the monitor panel. The former flashes when the inspired oxygen concentration is less than 21% v/v, and the latter when the minute volume differs from that set on the tidal volume and frequency controls of the ventilator by more than the predetermined tolerance (table I). The electro-luminescent panel is used to display tidal volume as a bargraph, and airway pressure or carbon dioxide concentration in analogue and digital form. The panel also displays in English text alarm situations and important aspects of machine function (fig. 5): these include the machine initial self-check programme and specific machine faults. Up to eight of the 31 possible alarm messages may be displayed at one time, the most important messages being situated at the top of the panel whilst the normal analogue display remains in the lower part of the panel.

TABLE I. *Warnings of departure from normal function*

Factor	Alarm activation
Group 1: Audible and visible alarm, by illuminated text on panel, together with message on Electroluminescent Panel (ELP).	
Low inspired oxygen	$< 21\%$ oxygen
High airway pressure	> 1.5 kPa for 3 s
Airway leak	$> 20\%$ of minute volume
(The above share a common two-tone audible alarm)	
Oxygen supply failed	$< 50\%$ of normal operating pressure
(The audible alarm is a Ritchie whistle)	
Group 2: Visible alarm only, by colour light on panel and message on ELP	
Nitrous oxide or air supply failed	$< 50\%$ of normal operating pressure
Group 3: Visible warning only, by flashing "Measured" LED and message on ELP	
	Difference between "set" and "measured" values exceeds:
Incorrect fresh gas flow	$\pm 10\%$ of set value ± 0.3 litre min^{-1}
Incorrect fresh gas O_2 %	$\pm 10\%$ of set value $\pm 5\%$ oxygen
Incorrect vapour (%)	$\pm 10\%$ of set value $\pm 0.5\%$ v/v
Low minute volume	-15% of set value
Group 4: Visible indication by message on ELP	
Electronic malfunctions	Error codes to assist diagnosis by a service engineer are displayed during the SELF TEST procedure

The number of combined audible and visual alarms has been deliberately kept to a minimum. The visual indicators for these alarms are grouped on the alarm panel and when activated are accompanied by a common audible alarm. The audible alarms are listed in table I. The audible alarm for airway leak can be inactivated for preset periods by repeated pressure on the mute button so that the alarm does not sound in situations when a large leak is expected (for example during an inhalation induction of anaesthesia). "System fault" in the microprocessor system is also provided with audible and visual alarms.

OTHER SAFETY FEATURES

Fresh gas concentrations and flows

There is a mechanically-operated oxygen flush control which is connected directly to the oxygen line and which provides a flow of 30–70 litre min^{-1} to the common gas outlet. A text warning is displayed on the E–L panel when the oxygen flush is activated.

The machine is designed to deliver a minimum oxygen flow of 1 litre min^{-1} and a minimum total fresh gas flow of 3 litre min^{-1}. However, when the carbon dioxide absorption system is selected, a "low flow option" is provided which permits the total fresh gas flow to be reduced to 2 litre min^{-1}. When this option is chosen, a yellow alert, "low flow selected", is illuminated.

The choice of a minimum fresh gas flow of 3 litre min^{-1} was based on four considerations:
(1) At fresh gas flows of 3 litre min^{-1} and greater, the concentration of vapour in the inspiratory limb of a circle system approximates closely to the concentration delivered from a vaporizer situated in the fresh gas supply line [13]. This obviates the need for a rapid analyser in the breathing system.
(2) When this fresh gas flow is used there is unlikely to be gross hypercapnia with any of the semi-closed breathing systems incorporated in the breathing system module (Sykes and colleagues, in preparation).
(3) The adoption of a minimum oxygen flow of 1 litre min^{-1} results in a fresh gas oxygen concentration of 50% v/v when the total flow of oxygen and nitrous oxide is 2 litre min^{-1}, 33% v/v when the flow is 3 litre min^{-1}, and 25% v/v when the flow is 4 litre min^{-1} and greater. These fresh gas oxygen concentrations ensure that the inspired oxygen in a circle absorption system remains

adequate despite variations in nitrous oxide uptake with time [14].

(4) Small leaks in the breathing system are less hazardous when fresh gas flow approaches the minute volume.

Gas and vapour analysis

Conventional electrochemical sensors for oxygen have a limited life and can fail in an unsafe mode [15], whilst currently available vapour analysers suitable for use in the breathing system are expensive, have a limited frequency response [16], and may be affected by water vapour. It was, therefore, decided to utilize a simple, stable and extremely reliable analyser to perform the gas and vapour analysis in the fresh gas system. By using the microprocessor to control sequential sampling from the fresh gas supply lines, the gas mixer output and the mixer output it has proved possible to use an automated interferometer to follow the gas mixing and vapour mixing process [9, 17]. Samples are taken sequentially from each of these sites at frequent intervals and the panel displays are updated continuously while gas is flowing to the patient. The interferometer samples also the gas inputs to the gas mixing unit and positively identifies these during the pre-use check procedure which is initiated when the mains supply is switched on. A paramagnetic oxygen analyser samples from the inspiratory limb of the breathing system to provide measurement of inspired oxygen concentration as this may differ from the fresh gas oxygen concentration. It is this analyser which activates the alarm and safety system when the inspired oxygen concentration decreases to less than 21% v/v.

Breathing systems

Bidirectional flow transducers are situated in the inspiratory and expiratory limbs of the breathing system. These enable inspired and expired tidal volumes to be monitored continously for detection of breathing system leaks. These flowmeters are used also to check that the APL valve does not leak during inspiration and that there is no malfunction of the gravity operated one-way valves used in the circle systems. Selection of "Common Gas Outlet" while retaining the normal twin hose breathing system also results in an alert signal.

Microprocessor system

Separate microprocessors are used to control the gas mixing, vaporizer and ventilator modules, and a fourth is dedicated to the gas analyser. Each of these is connected to the monitor microprocessor (fig. 7). In the event of catastrophic failure of the electronics system, or a simultaneous failure of the mains supply and back-up battery, the ventilator reverts to manually controlled or spontaneous breathing and the oxygen flush control continues to function normally. A more likely mode of failure would be the loss of one of the control modules (gas mixer, vaporizer or ventilator), or one of the two surveillance modules (gas analyser or monitor).

Recent modifications

During the course of the prolonged reliability and laboratory trials, a number of changes have been made to the major components which have been described in earlier papers [7–9].

(a) *Gas mixing device*. Hazard and risk analysis revealed the need to include a further solenoid valve in the nitrous oxide supply. This valve is of the "normally closed" type and is held open only when a signal from the gas analyser confirms that the oxygen concentration in the mixed gas exceeds 21% v/v. This system protects the patient in the event of the pulsing solenoid failing open and also meets the ISO standard for a nitrous oxide cut-off device to operate in the event of oxygen supply failure.

Trials of the lung ventilator revealed that the original gas mixing system had excessive internal compliance. This resulted in the fresh gas flow being distorted by the back-pressure generated by IPPV in the breathing system, so that flow was reduced considerably during the inspiratory phase and increased during the expiratory phase. The effect on oxygen provision and carbon dioxide elimination was unpredictable, but clearly unacceptable.

The problem was overcome by reducing the scale of the flow-surge damper chambers and eliminating the spring-loaded diaphragms. However, in order to restore an acceptable level of flow-surge absorption, it was necessary to reduce the pulse size at low flows. The final system changes the pulse/frequency programme at three stages as flow is increased from the 2-litre min^{-1} minimum to 20-litre min^{-1} maximum.

(b) *Vaporizer system*. Possibly the most serious hazard associated with an anaesthetic apparatus is the ingress of liquid anaesthetic agents into the breathing system. Because of this risk, we decided

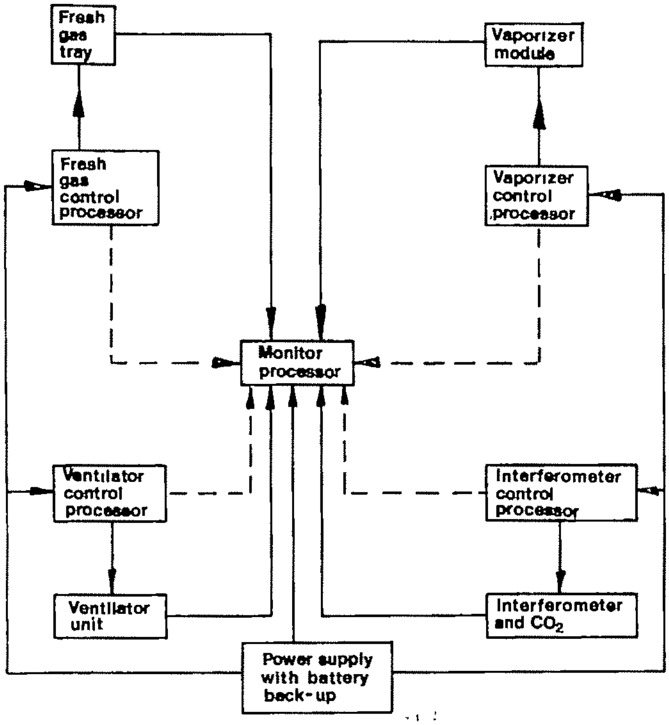
Fresh gas tray
Vaporizer module
Fresh gas control processor
Vaporizer control processor
Monitor processor
Ventilator control processor
Interferometer control processor
Ventilator unit
Interferometer and CO_2
Power supply with battery back-up

FIG. 7. Microprocessor communication system.

that our otherwise attractive system of gravity feed to the vaporizers from the original drug bottles was suspect. When we found in practice that these bottles, which are of ordinary commercial quality, could not be relied upon to seal satisfactorily to the filling connections, we decided that the system had to be abandoned. In its place, we now use conventional reservoirs, level with the vaporizers and connected to them by small-bore pipes to prevent the solution of nitrous oxide in the liquid [18]. Conventional or keyed fillers can be provided, and the liquid level is displayed by glass tube indictors close to the filling orifices and by electronic level indictors below the main control panel.

(c) *Interferometer*. The successful development of the automated interferometer proved to be technically demanding, and involved many disciplines. As a result, the interference image has been improved greatly and it is now possible to operate the unit with 40 pixels separating each peak, in place of the original 20, thus doubling the basic sensitivity. Reliable recognition of the principal peaks, even in the presence of optical and electronic distortions, was achieved by the use of an algorithm developed by Jeavons [19].

DISCUSSION

Cooper and colleagues [20] were the first to describe a radically new approach to a nitrous oxide–oxygen–anaesthetic vapour delivery system. Their prototype utilized a microcomputer to drive digital gas mixing valves and a liquid anaesthetic injector system for delivery of anaesthetic vapours. Gas delivery to the patient was via a Mapleson D system and alarm and warning messages were displayed to guide the operator in use. Wallroth [21] has described another approach which is based on the use of the circle carbon dioxide absorption system. The present machine is based on similar design concepts, but utilizes different technology to achieve greater versatility and improved monitoring of the machine functions. A special emphasis has also been given to ergonomic considerations [22].

The charge might be made that the increased complexity of the technology utilized in the present machine would add the hazard of increased unreliability, when compared with conventional mechanical counterparts. For this reason, extreme care has been taken in the design and testing of the components. For example, the solenoid valves are designed to undertake 10^8 operations without failure, and a number of batches have been tested for much longer periods. This number of operations represents 5 years of running 8 h a day for 6 days a week, but it is planned to replace these valves at the yearly service to ensure an even greater margin of safety.

Faults in the microprocessors can also be a problem. These may be caused by external interference from diathermy or other electromagnetic sources, by latent software errors or by internal malfunction. To overcome these problems, all the five microprocessors controlling the gas mixing, gas analysis, ventilator and monitor functions have been linked through opto-isolator circuits and are under the surveillance of a software system which checks continuously on their performance (fig. 7). The most likely problem is a transient caused by high levels of electromagnetic interference from diathermy, x-ray machines and similar sources. Transient disturbances, although causing no permanent damage, can disrupt the flow of the programme in a microprocessor, causing a total loss of function. To detect such a fault, the programme regularly passes through a sequence of check points: failure to reach a checkpoint within 0.1 s activates a reset circuit and invokes an automatic software recovery procedure. In tests with simulated transient errors, normal operation was restored within a fraction of a second in 98.7% of cases [23]. It is worth recording that the man–hours expended in building and testing the additional reliability and safety factors, following a formal Reliability Engineering procedure [24], far exceeded those taken to produce the initial prototype.

One final advantage of microprocessor control is that electrical outputs for all monitored functions are available and can be used to provide the basis for a comprehensive anaesthetic record system.

ACKNOWLEDGEMENTS

The project was made possible by the award of a Microprocessor Development Grant from the Department of Industry, and financial support from the Department of Health and Social Security. The authors also wish to acknowledge the help of other members of the Nuffield Department of Anaesthetics and Penlon Ltd, who worked on the project for varying periods. In particular, thanks are due to Dr W. L. Davies, Senior Physicist in the Nuffield Department of Anaesthetics, Mr P. J. Tyrell, Department of Engineering, Mr J. Blond, Department of Physics, Oxford Polytechnic and Mr A. J. Hillier, Managing Director, Penlon Ltd.

Note added in proof: Although clinical trials have validated the concepts incorporated in this apparatus, Penlon Ltd have recently decided, on commercial grounds, not to proceed with production of the machine.

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RESISTANCE TO AIRFLOW IN ANAESTHETIC BREATHING SYSTEMS

D. G. MARTIN, K. L. KONG AND G. T. R. LEWIS

SUMMARY

We have examined, under reproducible conditions, the resistance to airflow of complete anaesthetic breathing systems (Magill, Coaxial Lack, Parallel Lack and Bain systems) and components of these systems. All systems had resistances within the recommended ranges at all flows likely to be experienced in normal clinical practice. The Magill system had the lowest resistance under all conditions. It is concluded that comparisons should be made only between complete breathing systems.

The resistance to airflow of the components of breathing systems have been examined previously. Tracheal tubes and their connectors have been studied by a number of authors [1,2] and expiratory valves by others [3,4]. Smith [5] examined the resistance of the Magill system for both separate and assembled components. Shandro [6] studied the Ayre's T-piece, Bain and several circle systems.

Several new breathing systems have been developed in recent years, and changes have been introduced, into both the design of their components and the materials used. These changes may have affected the resistance to gas flow.

The aim of this study was to investigate the resistance to airflow in some of the commonly used anaesthetic breathing systems under standardized conditions.

METHODS

The apparatus used to measure resistance to airflow was described by Gaensler and colleagues [7] and is shown in figure 1.

Air was supplied from a cylinder through a variable pressure regulator (Murex Saffire BS 5741). The airflow rate was controlled by a needle valve and measured by a flowmeter (Platon Gap Meter type GTLK laboratory flow meter). The air was passed into a 10-litre glass bottle, which was used to avoid any Venturi effect [8]. The outlet of this bottle was fitted with a standard 22-mm male connector, to which apparatus under investigation was connected either directly or via a 22-mm female–female adaptor. The inside of the glass bottle was connected by a tube to one limb of a U-tube manometer, the other limb of which was open to the atmosphere. Thus this manometer measured the changes in pressure produced by air

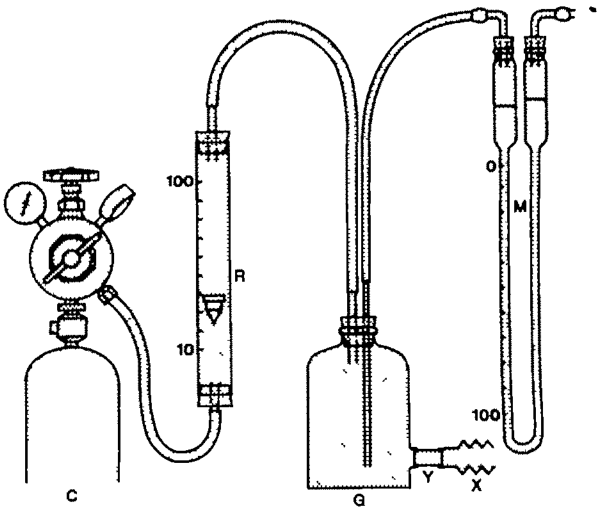

FIG. 1. Apparatus for measuring the pressure changes produced by airflow through the breathing systems. C = Cylinder of air; R = rotameter; G = glass jar; M = manometer; X = piece of apparatus examined; Y = 22-mm male connector.

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flowing through the apparatus under test. The U-tube manometer used was accurate to ±10 Pa. In the case of the corrugated and smooth-bore breathing tubes, angle piece and catheter mount, an inclined angle manometer accurate to ±5 Pa was used.

All the tests were conducted at 20 (SD 3) °C after the apparatus had been equilibrated at that temperature for at least 1 h. Flow rates of 10–100 litre min^{-1} in ascending and then descending steps of 10 litre min^{-1} were used. Each reading was taken after allowing the pressure in the apparatus to stabilize for at least 30 s. The reading at each flow step was repeated three times and the average of the sets of readings obtained was taken.

The tests were carried out with the breathing system laid out straight and unstretched on a bench and repeated with the system coiled once through 360° around a 5-cm diameter mandrel.

The specifications of the breathing apparatus examined are shown in table I. The direction of gas flow through the systems during inspiration and expiration is demonstrated in figure 2.

RESULTS

It was found that a breathing system composed of the same set of components produced consistent results on different days with barometric pressures of 750–780 mg Hg. However, there was a variable increase in the pressure changes during

TABLE I. *Dimensions of breathing systems studied. Lack 1 = Coaxial Lack system (MIE Ltd); Lack 2 = Parallel Lack system (Tricomed Ltd); Bain manufactured by Blease Medical Ltd. *Allowing for the cross-sectional area of the inner tube (outer diameter of inner tube = 19 mm in Lack 1 system and 10 mm in Bain system)*

System	Minimum internal diameter (mm) Insp.	Exp.	Minimum cross-sectional area (mm^2) Insp.	Exp	Length (cm)
Magill	22	22	380	380	107
Lack 1	28	15	332*	177	150
Lack 2	15	15	177	177	150
Bain	22	22	302*	302*	180

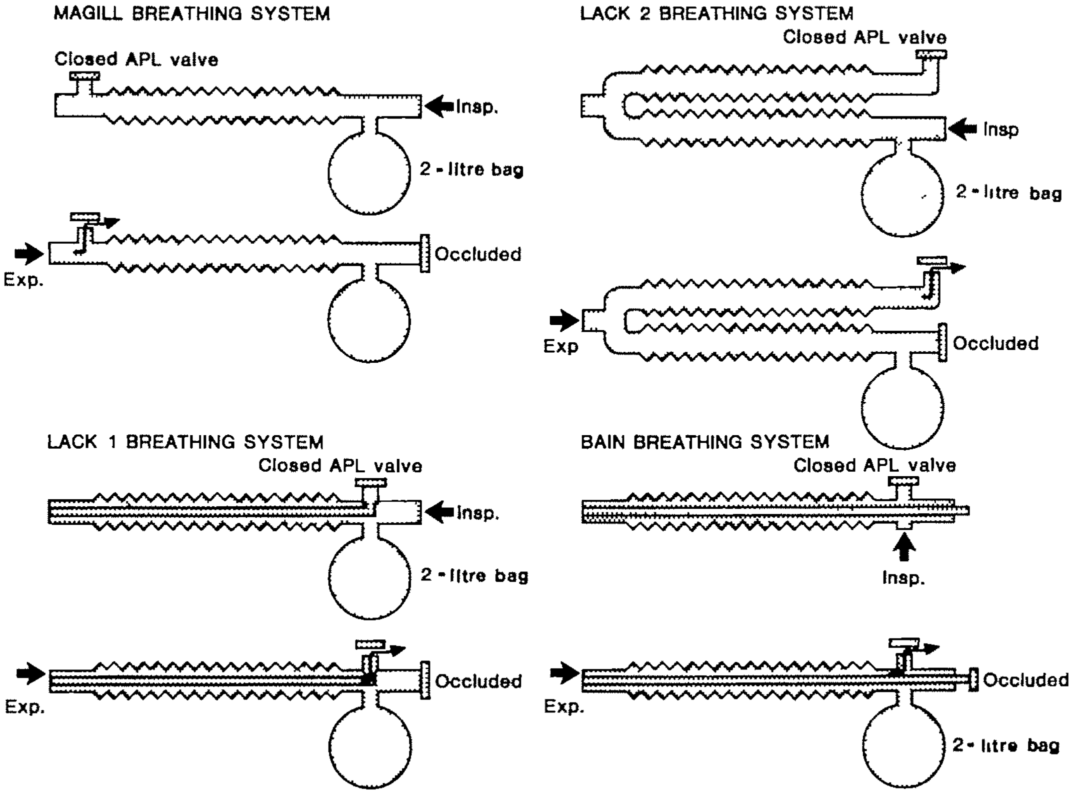

FIG. 2. Direction of airflow through the breathing systems in inspiratory and expiratory modes.

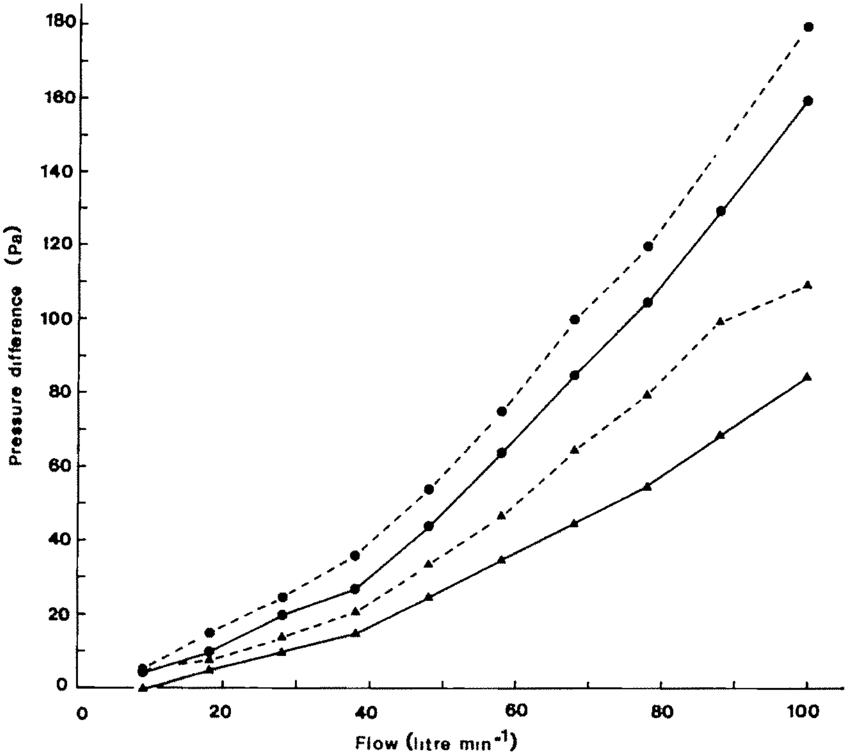

FIG. 3. Pressure differences produced by airflow through corrugated tubes (internal diameter 22 mm): straight ▲——▲ or coiled ▲---▲; and smooth bore Rusch tubes (internal diameter 15 mm): straight ●——● or coiled ●---●.

air flow in sets of a breathing system with different degrees of use. Therefore, unused breathing systems were used throughout this study.

The pressure changes produced by air flowing through the corrugated and smooth-bore tubes are shown in figure 3.

The pressure changes in the Magill, Lack 1 (Coaxial) and 2 (Parallel) and Bain systems produced by air flow in the inspiratory and expiratory directions are shown in figures 4–7. The results presented were obtained with the adjustable pressure limiting (APL) valve closed in the inspiratory mode and open in the expiratory mode. It was found that, in the inspiratory mode, there was no difference in the values obtained with the APL valve open and closed, except at very high flows in systems including the catheter mount when high pressures were generated.

The pressure changes obtained with the breathing systems at air flows of 10, 30 and 60 litre min^{-1} are summarized in table II.

The gradients of the relationship between log pressure and log flow are shown in table III. These were obtained by calculating the regession equation of the line. The gradients of log pressure difference against log flow can be used to determine whether flow is laminar, transitional or turbulent (see Appendix).

TABLE II. *Pressure differences (Pa) in the breathing systems (straight)*

	System			
	Magill	Lack 1	Lack 2	Bain
Inspiratory flow				
10	0	10	10	13
30	13	33	65	85
60	60	113	345	315
Expiratory flow				
10	80	85	90	90
30	170	195	200	200
60	285	380	463	475

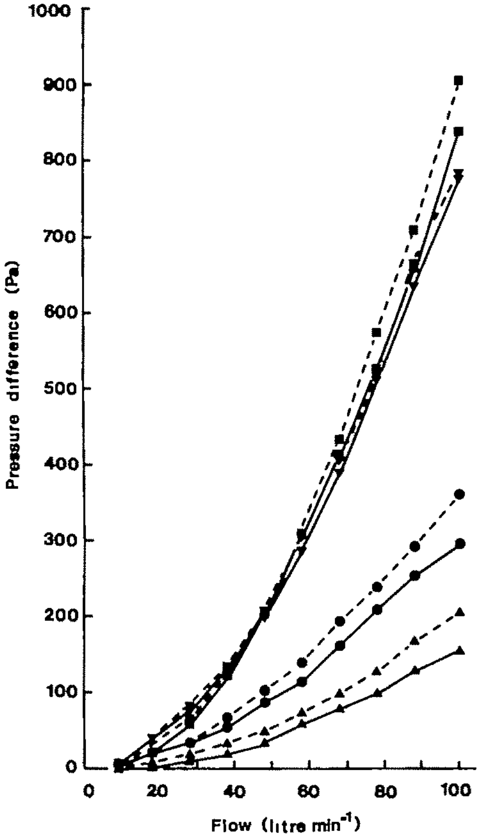

FIG. 4. Pressure differences produced by airflow through straight (——) and coiled (---) breathing systems (inspiratory mode): Magill (▲); Lack 1 (●); Lack 2 (■); Bain (▼).

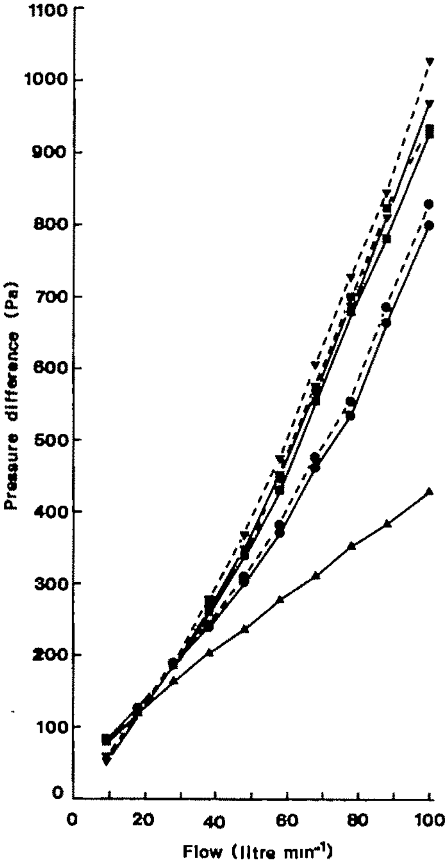

FIG. 5. Pressure differences produced by airflow through straight (——) or coiled (---) breathing systems (expiratory mode): Magill (▲); Lack 1 (●); Lack 2 (■) and Bain (▼).

DISCUSSION

Breathing systems should be studied as a whole when considering their resistance to breathing. When a number of resistors are joined to form a breathing system they interact in a complex manner. Adjacent components may have unpredictable effects on the resistance to air flow in each other [9]. Thus the total resistance of a breathing system is not the simple sum of the resistances of its component parts. This complex interaction is demonstrated clearly by the effects of adding a catheter mount or angle piece to the system.

It may be seen from the gradients of the log–log plots (table III) that the flow in anaesthetic breathing systems was almost exclusively turbulent in the direction of inspiratory flow (see Appendix). The pressure changes in anaesthetic breathing systems depend, therefore, on the density of the gas rather than its viscosity, in addition to the diameter and length of the tubes. However, the flow in the expiratory direction appears to be less turbulent. This is because the expiratory valve opens progressively as flow increases, tending to produce a constant pressure difference, thus reducing the gradient of the log

TABLE III. *Gradients (SD) of log pressure against log flow plots (for straight breathing systems)*

System	Inspiration	Expiration
Magill	2.17 (0.069)	0.807 (0.005)
Lack 1	1.52 (0.054)	1.19 (0.036)
Lack 2	2.05 (0.035)	1.37 (0.019)
Bain	1.78 (0.018)	1.37 (0.022)

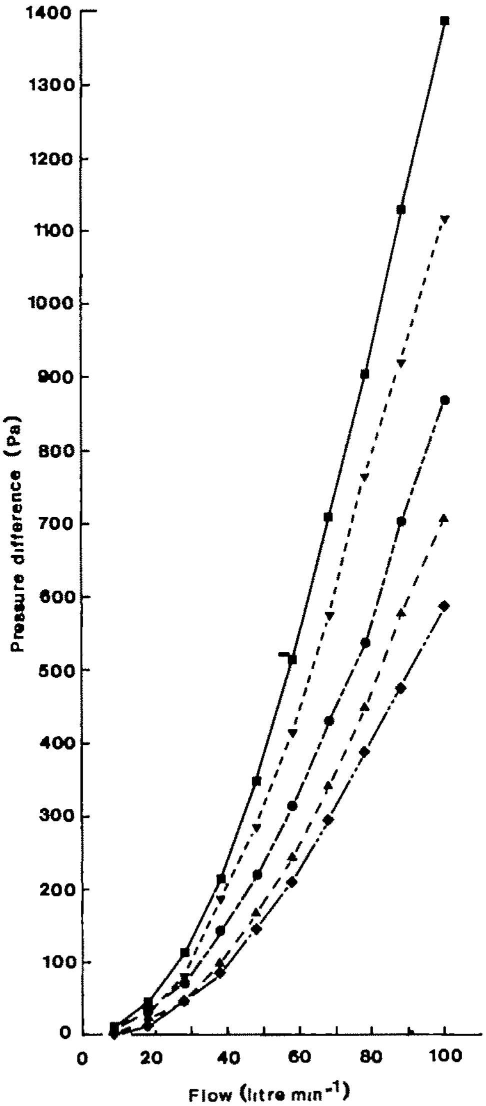

FIG. 6. Pressure differences produced by airflow through catheter mount (◆) and breathing system plus catheter mount (inspiratory mode): Magill system (▲); Lack 1 system (●); Lack 2 system (■); Bain system (▼).

pressure–log flow relationship of the system. The effect of the expiratory valve alone is demonstrated clearly in the Magill system in expiration, resulting in a gradient of less than 1. It was noted that the log pressure–log flow plots showed no sudden change in gradient, suggesting that the expiratory valves are not open fully at flow rates of up to 100 litre min^{-1}. Our results (table II) showed that the expiratory valves in the systems studied have remarkably low opening pressures of less than 80 Pa and resistances of only 125–150 Pa at flows of 30 litre min^{-1}. These results are similar to those described by Nott and Norman [4].

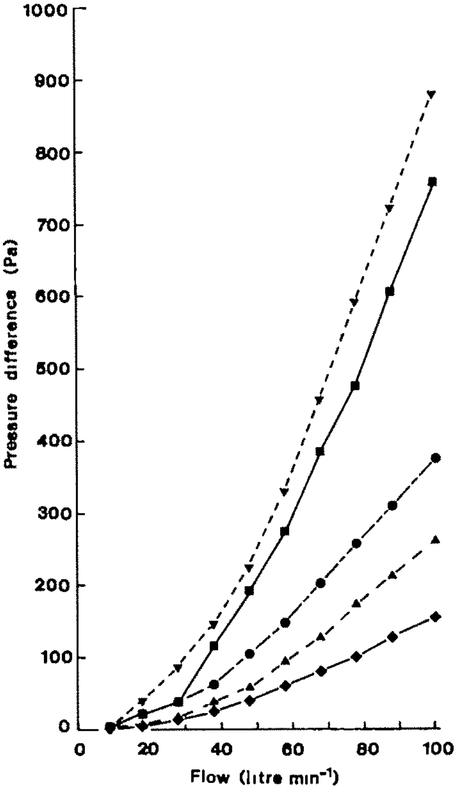

FIG. 7. Pressure differences produced by airflow through angle piece (◆) and breathing systems plus angle piece (inspiratory mode): Magill system (▲); Lack 1 system (●); Lack 2 system (■); Bain system (▼).

The increased work of breathing produced by anaesthetic breathing systems has been regarded as a more relevant measure of their suitability [5,10]. However, the work of breathing is a function of the pressure difference across the resistance [11] and there is little difference in the clinical value of data obtained from the work of breathing and that from the resistance to air flow [5]. As it is difficult to produce a standardized sinusoidal gas flow [5], the pressure changes produced by the resistance of a system to continuous air flow is the most practical measure when comparing breathing systems under standardized conditions.

Nunn [12] has suggested that pressures greater than 3 cm H_2O (294 Pa) at flows of 30 litre min^{-1}

and 6 cm H_2O (588 Pa) at flows of 60 litre min^{-1} represent excessively high resistances, likely to produce physiological disturbances. This study shows that only relatively small changes in pressure occur at gas flows within the physiological range in all the systems investigated. However, it must be remembered that, in the typical anaesthetized patient, the total resistance to breathing may be much higher because of the extra resistance of tracheal tubes and that of the patient's bronchial tree.

APPENDIX

Reynolds [13] postulated a general law for all types of flow in a system:

$$\left(\frac{k_1 P r^3}{nu^2}\right) = \left(\frac{k_2 r \bar{u}}{nu}\right)^n$$

where k_1 and k_2 are constants; nu = kinematic viscosity (η/ρ); $\bar{u}$ = mean velocity; p = pressure needed to maintain a constant flow; r = radius of the tube; n = a variable exponent which has the value 1.0 for laminar flow and 2.0 for turbulent flow.

The above equations are stated in terms of $\bar{u}$, the linear velocity. They can be restated in terms of flow rate by volume $\dot{V}$, where $\dot{V}$ is $\pi r^2 \bar{u}$ units per unit of time:

$$\left(\frac{k_1 P r^3}{nu^2}\right) = \left(\frac{k_2 \dot{V}}{\pi n u r}\right)^n$$

thus $$P \alpha \dot{V}^n$$

thus $$\log P \alpha n \log \dot{V}$$

therefore, if log P is plotted against log $\dot{V}$, the gradient of the line through these points is n. If $n = 1.0$, flow is laminar; if $n = 2.0$, flow is turbulent.

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CONTROLLED VENTILATION WITH A MAPLESON A (MAGILL) BREATHING SYSTEM: REASSESSMENT USING A LUNG MODEL

C. K. G. TYLER, P. K. BARNES AND M. P. RAFFERTY

SUMMARY

We have used a lung model to reassess the efficiency of the Magill attachment during controlled ventilation in which the pattern of ventilation, tidal volume and fresh gas flows were varied. Adjustment of the inspiratory: expiratory ratio to ensure a prolonged expiratory phase is recommended, to improve efficiency and predictability of the system, if its use is necessary for short periods during controlled ventilation in clinical practice.

The Magill attachment was introduced, approximately 60 years ago, to provide an efficient system for spontaneous ventilation, with facility for providing intermittent positive pressure ventilation in an emergency [1]. The inefficiency of the system has been documented clearly in respect of carbon dioxide elimination during controlled ventilation [2]. Marshall and Henderson [3] reported that, in spite of the presence of rebreathing, it was possible to reduce arterial carbon dioxide concentrations when using the Magill attachment for controlled ventilation with fresh gas flows far smaller than those suggested by Sykes [2], if the level of ventilation was increased. This report and our own clinical observations stimulated us to re-evaluate the Magill system during controlled ventilation.

We have used a lung model to reassess the efficiency of the Magill attachment when used for intermittent positive pressure ventilation. We have examined the effect of varying the inspiratory: expiratory ratio when the pattern of ventilation, tidal volume and fresh gas flows were varied.

METHODS

The arrangement of apparatus used in this experiment is shown diagrammatically in figure 1. A standard Magill attachment was used, with a 2-litre reservoir bag enclosed in an aspirator bottle. A Servo 900C ventilator was connected to this bottle so that the desired pattern of controlled ventilation could be simulated. The Heidbrink valve was connected via a Fleisch pneumotachograph head to a non-compliant deadspace tubing of 130 ml, and thence to an electronic Wright's Respirometer (Ohmeda) and the lung simulator (Ohmeda). The compliance of the lung was set at 50 ml/cm H_2O and the resistance at 5 cm H_2O litre^{-1} s^{-1}. The accuracy of these settings was confirmed using a water manometer. A continuous flow of carbon dioxide 210 ml min^{-1} was supplied to the centre of the lung. The fresh gas supply to the Magill attachment was carbon dioxide-free compressed air. The gas flow to the Magill attachment and the carbon dioxide supply to the lung model was supplied by universal rotameters (Gapmeter Lab Kits – A6) which had been calibrated previously against a spirometer of known accuracy (Ohio 840). The Heidbrink valve in the system was checked to comply with the specification of Nunn [4], measured by a method previously described [5]. It was adjusted so that all the desired patterns of ventilation could be achieved and remained in this position throughout the experiment. Five sampling lines were incorporated into the system (fig. 1).

Gas analysis from the sample sites was performed by mass spectrometry (Centronic 200

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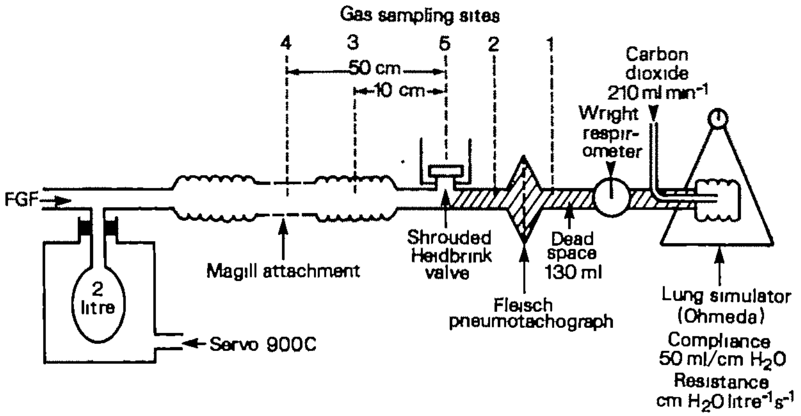

FIG. 1. Schematic diagram of apparatus.

MGA). The readings were displayed graphically on a chart recorder (Brush 200 Gould), simultaneously with flow patterns measured by the Fleisch pneumotachograph.

The system was checked to ensure that it was leak-proof before and after each series of readings, by using a soap film technique. Gas was collected from the Heidbrink valve into a spirometer and compared with the volume of fresh gas and carbon dioxide supplied to the system. During the experiment the ventilatory rate was 15 b.p.m. and peak pressure within the system did not exceed 20 cm H_2O.

Three experiments were performed.

Experiment A

The lung model was ventilated with a fresh gas flow of 10 litre min^{-1} and an inspiratory: expiratory ratio of 1:4. The effect of changing from a ramp to a square inspiratory waveform was studied at tidal volumes of 300–700 ml.

Experiment B

The lung model was ventilated with a fresh gas flow of 10 litre min^{-1} and with a square inspiratory waveform. Tidal volume was varied between 300–700 ml with an inspiratory: expiratory ratio from 1:1 to 1:4.

Experiment C

The lung model was ventilated with a square inspiratory waveform and a tidal volume of 500 ml. The fresh gas flow was varied between 9 litre min^{-1} and 13 litre min^{-1} and the effect of varying the inspiratory: expiratory ratio from 1:1 to 1:3 was studied.

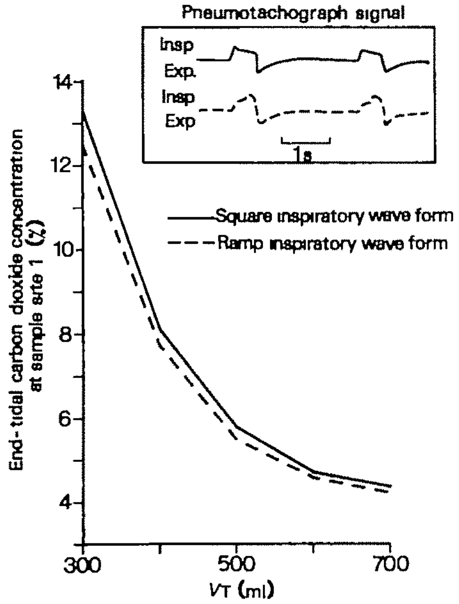

FIG. 2. End-tidal carbon dioxide concentrations using ramp and square inspiratory waveforms.

RESULTS

The response time of the pneumotachograph was found to be less than 10 ms and that of the mass spectrometer 150 ms. The positions of the simultaneous recordings were adjusted for this time lag before analysis.

Experiment A

The effect of ventilating the Magill breathing system with a ramp and a square inspiratory waveform produced no difference in the end-

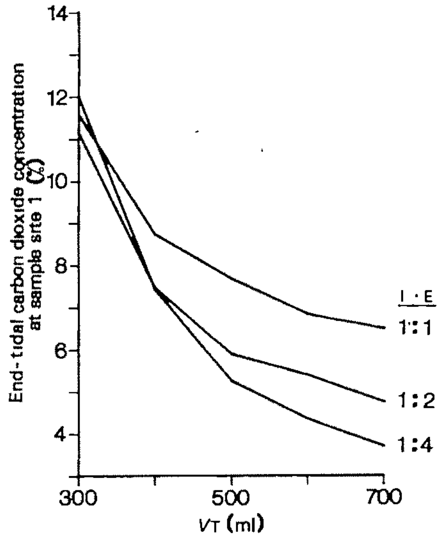

FIG. 3. The effect of varying tidal volumes on end-tidal carbon dioxide concentration with different inspiratory: expiratory ratios.

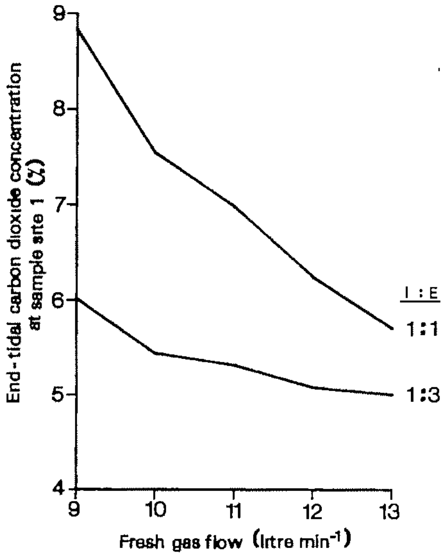

FIG. 4. The effect of varying fresh gas flow on end-tidal carbon dioxide concentration with different inspiratory: expiratory ratios.

tidal carbon dioxide concentration when the tidal volume was varied between 300 and 700 ml (fig. 2).

Experiment B

At low tidal volumes, there was not difference in end-tidal carbon dioxide concentrations when the inspiratory:expiratory ratio was varied. As tidal volume was increased, the end-tidal carbon dioxide concentration decreased. The concentration of carbon dioxide for any given tidal volume was lower with an inspiratory:expiratory ratio of 1:4 (fig. 3).

Experiment C

With a fresh gas flow of 9 litre min^{-1}, the end-tidal carbon dioxide concentration was lower when the inspiratory:expiratory ratio was 1:3. As the fresh gas flow was increased, the end-tidal carbon dioxide concentration decreased. At all fresh gas flows, the end-tidal carbon dioxide concentration was lower with an inspiratory:expiratory ratio of 1:3 (fig. 4).

DISCUSSION

A change from ramp to square inspiratory waveform did not affect the elimination of carbon dioxide from the Magill attachment during controlled ventilation. If the tidal volume or fresh gas flow was increased, the system became more efficient in respect of carbon dioxide removal. These findings confirm those reported previously [2]. However, at any given tidal volume or fresh gas flow, the system became more efficient as the expiratory phase was prolonged. When controlled ventilation with an inspiratory:expiratory ratio of 1:3 was used, the system was efficient when a fresh gas flow of 9 litre min^{-1} was supplied at a tidal volume of 500 ml. As fresh gas flow was increased at this inspiratory:expiratory ratio, relatively little was gained in the efficiency of carbon dioxide removal from the system. When an inspiratory:expiratory ratio of 1:1 was used, however, high fresh gas flows were needed to achieve an acceptable inspired concentration of carbon dioxide.

When the Magill attachment is used for controlled ventilation, the Heidbrink valve is closed sufficiently to allow positive pressure to be applied to the reservoir bag to ventilate the patient's lungs. During the inspiratory phase, gas is forced through the Heidbrink valve. The escape of gas ceases when the pressure decreases sufficiently during expiration for the valve to close. Once the valve has closed, expiratory gases pass retrogradely up the circuit. Failure of the elimination of this expired gas from the circuit is the cause of rebreathing [2]. A comparison of the carbon dioxide concentrations measured from all the

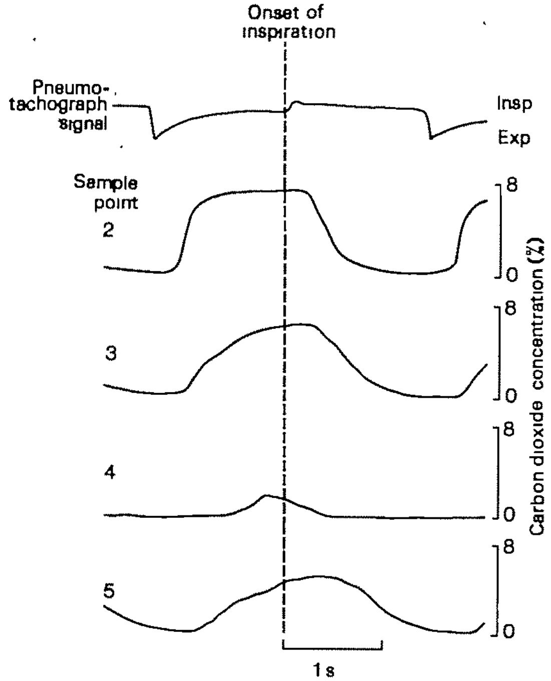

FIG. 5. Synchronous display of gas flow and carbon dioxide concentrations at sampling sites 2–5 with an inspiratory: expiratory ratio of 1:1; tidal volume 500 ml; fresh gas flow 10 litre min^{-1}; ventilatory frequency 15 b.p.m.

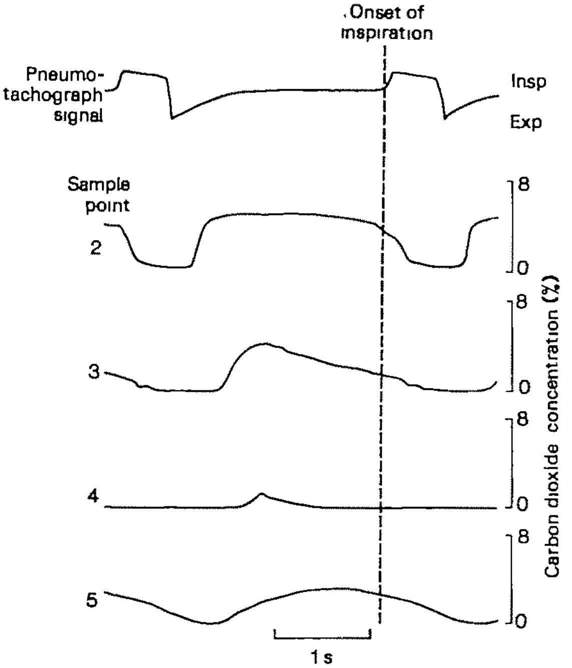

FIG. 6. Synchronous display of gas flow and carbon dioxide concentrations at sampling sites 2–5 with an inspiratory: expiratory ratio of 1:4; tidal volume 500 ml; fresh gas flow 10 litre min^{-1}, ventilatory frequency 15 b.p.m.

sampling sites during a single ventilatory cycle at inspiratory:expiratory ratios of 1:1 and 1:4 illustrates what happens to this expired gas.

In figure 5, carbon dioxide concentrations at sample points 2–5 (see figure 1) are shown, timed with the pneumotachograph signal. In this instance the inspiratory:expiratory ratio was 1:1. At the beginning of inspiration, carbon dioxide is present at sampling sites 4 and 3 (fig. 1). This is carbon dioxide which has passed retrogradely during expiration and has failed to be cleared from the breathing system. The bulk of carbon dioxide elimination via the Heidbrink valve occurs during inspiration, as indicated by the high concentration at sample site 5 (fig. 1). The same sequence of events can be seen in figure 6, when the inspiratory:expiratory ratio was 1:4. Here the bulk elimination of carbon dioxide from the circuit occurs during the expiratory phase. Carbon dioxide is cleared more efficiently from the system, as can be seen by reference to the carbon dioxide concentrations at sample point 4, which is zero and sample point 3, which is just over 1%. The net result of using the inspiratory:expiratory ratio of 1:4 at any given tidal volume and fresh gas flow is to allow a longer period of exhaled carbon dioxide to be flushed from the system by fresh gas flow.

Because the composition of vented and inspired gas can be affected by so many variables, the Magill attachment must be considered a system with a largely unpredictable performance when used during controlled ventilation. This unpredictability can be overcome by monitoring inspired gas concentrations. We do not recommend that the Magill attachment is used for controlled ventilation, but when it is used for short periods in clinical practice, improved efficiency can be obtained by adjusting the inspiratory:expiratory ratio to ensure a prolonged expiratory phase.

ACKNOWLEDGEMENT

The authors wish to acknowledge the part played by the late Professor C. M. Conway in the preparation of the procedure for this study, and his involvement in the early discussions of the results.

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Br. J. Anaesth. (1989), 62, 467–470

CORRESPONDENCE

ADVERSE REACTIONS TO ATRACURIUM

Sir,—The recent report of a severe adverse reaction to atracurium [1] has prompted us to report two further severe reactions to this drug.

An obese 9-yr-old 45-kg boy was admitted to our hospital unconscious with a closed head injury and a fractured right elbow. A CT scan showed diffuse brain injuries and surgery was planned to insert a ventricular drain for intracranial pressure monitoring. The patient had no significant past medical history except for occasional "asthma attacks" which did not require admission to hospital. Anaesthesia comprised thiopentone 250 mg, suxamethonium 5 mg, alcuronium 20 mg, nitrous oxide and oxygen, and increments of fentanyl 50 µg. He was admitted to the ICU after operation for 4 days.

Elective surgery for internal fixation of the right elbow was planned 10 days after admission. No premedication was given. Anaesthesia was induced with thiopentone 250 mg, followed by atracurium 20 mg after flushing the i.v. cannula with normal saline. Tracheal intubation was undertaken without difficulty. However, attempts to ventilate the lungs using a Magill system proved impossible. A diagnosis of severe bronchospasm was made after exclusion of tube obstruction. The patient rapidly became extremely cyanosed and developed bradycardia. Four millilitre of 1:10 000 adrenaline was given i.v. Manual ventilation of the lungs with 100% oxygen became easier almost immediately and the patient's colour improved. Throughout this period of approximately 20 min, the carotid and femoral pulses remained palpable, but surgery was abandoned and the patient was admitted to the ICU. Approximately 4 h after the adverse reaction, he was awake and orientated. Chest x-ray was normal.

Surgery was re-scheduled to take place 3 days later. After oral premedication with diazepam 10 mg, anaesthesia was induced with nitrous oxide, oxygen and halothane and tracheal intubation was accomplished without difficulty. Alcuronium 15 mg was given and anaesthesia was maintained with nitrous oxide, oxygen and supplements of fentanyl. Anaesthesia and surgery proceeded uneventfully. Intradermal testing was carried out 1 month later as described by Fisher [2]. Dilutions of thiopenone 1:100, atracurium 1:1000 and normal saline were used. The intradermal tests were negative after 30 min and the patient was again tested with atracurium diluted to 1:100, but again he showed no positive response.

Our second report is of a healthy 58-yr-old 50-kg woman (with no history of any significant previous illnesses) scheduled for elective total hip replacement. After premedication with oral diazepam 5 mg, thiopentone 200 mg was given, followed by a flushing dose of normal saline, atracurium 25 mg and tracheal intubation. Anaesthesia was maintained with nitrous oxide, oxygen and morphine supplements, 0.5% isoflurane and an infusion of atracurium 10 mg kg^{-1}. Approximately 2.5 h after induction of anaesthesia, her systolic arterial pressure decreased inexplicably and suddenly to 60 mm Hg. Blood loss had been insignificant, she had received adequate fluids and a second unit of blood was being infused. The ECG monitor showed normal sinus rhythm and polymethyl methacrylate cement had not yet been applied. The end-tidal carbon dioxide concentration was unchanged, the patient appeared flushed and warm, and the ears and hands became markedly oedematous and hyperaemic. A tentative diagnosis of adverse reaction to blood transfusion was made.

Blood transfusion was stopped, additional volumes of Hartmann's solution were infused, and the isoflurane discontinued. Hydrocortisone 100 mg and chlorpheniramine 5 mg were given i.v. The systolic arterial pressure gradually improved to 100 mm Hg over the next 30 min and surgery proceeded uneventfully. After operation she was admitted to the ICU, where she remained well. The blood used for transfusion showed no haematological incompatibility and no irregular alloantibodies were detected in the patient's serum. Four hours after the onset of acute hypotension blood was assayed for plasma immunoglobulin and complement C3 and C4 concentrations, but these were within the given normal range. One month later, intradermal skin testing was carried out for thiopentone and atracurium, with normal saline as a control. A florid positive reaction was seen with atracurium diluted 1:1000.

Nine previous communications have reported severe adverse reactions to atracurium [3]. Of our two patients, only the second showed a positive response to intradermal testing. Although there is no evidence that severe anaphylactoid reactions can be produced by histamine release in response to drugs given in normal doses, or that direct histamine release in response to drugs can produce severe bronchospasm [3], our first patient was very similar to the report by Stirton-Hopkins [1], where severe life-threatening bronchospasm followed the administration of atracurium to a patient with a history of eczema and asthma. Curiously, immediate cardiovascular collapse was not a feature in our first patient.

We note the view shared by Fisher [4] and by Rowlands [5] that "modification in anaesthetic technique based on the history of allergy, atopy or asthma is unlikely to reduce the likelihood of severe clinical anaphylaxis". Nevertheless, we believe that the severe bronchospasm in our first patient resulted from histamine release, and atracurium should probably be avoided in such patients. The acute hypotension in our second patient was probably an anaphylactoid reaction to atracurium, as suggested by the intradermal testing. The clinical features of oedema, and warm vasodilated peripheries have been described previously. Interestingly, the onset was delayed and did not occur at induction, but this is not a unique feature [6].

Our two case reports support the usefulness of intradermal skin testing if clinical anaphylaxis occurs following administration of a number of drugs. Measurement of plasma immunoglobulin and complement C3 and C4 concentrations was not useful in our second patient. This was not unexpected, as a moderate amount of blood had been lost and approximately 2 litre of crystalloids had been infused. Once again, the importance of administering adrenaline without delay in severe life-threatening clinical anaphylaxis is evident.

T. E. Oh
J. M. Horton
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SUXAMETHONIUM AND MALIGNANT HYPERTHERMIA

SIR,—The letter by Dr Nelson [1] concerning the *in vitro* response of human skeletal muscle to suxamethonium deserves comment. Dr Nelson reports that skeletal muscle from three family members testing positive for malignant hyperthermia (MH) responded with contractures when challenged with suxamethonium 5 (one patient) or 50 (two patients) mmol litre^{-1}. He states that "Further studies are needed to clarify these effects of suxamethonium on MHS muscle". The results reported contrast with those from Dr Denborough's laboratory [2], with our own results [3, 4] and with the results of several other investigators [see 3, 5]. Dr Nelson also reports that gracilis muscle from four MH susceptible pigs exhibited contracture responses to suxamethonium 50 mmol litre^{-1} [1]. This is in contrast to Dr Denborough's [2] results and our negative findings with gracilis muscle from six pigs (F1 generation from a Yorkshire × Duroc cross) challenged *in vivo* with halothane to verify MH susceptibility (unpublished studies).

The results obtained by Dr Nelson in porcine muscle *in vitro* may be explained by differences between breeds in muscle responses to agents associated with MH, as suggested in his letter. An example of a possible breed difference in response to halothane has been reported by Gallant [6]. In this latter study, halothane caused a small plasmalemmal depolarization in muscle from MH-susceptible Poland China pigs. However, this depolarization was not observed in MH-susceptible Pietrain pigs. Certainly, Dr Nelson's results obtained in the pig cannot relate specifically to MH, as some breeds do not show a contracture to suxamethonium. Perhaps the response to suxamethonium is the manifestation of some other skeletal muscle correlate of the MH defect expressed only in the breed used by Dr Nelson.

We know that skeletal muscle (diaphragm) from animals not susceptible to MH can exhibit contractures to suxamethonium. Previously we have reported occasional contractures to suxamethonium in rat diaphragm preparations [7] and, more recently, we have observed consistent and large (25–33% twitch height) contractures to suxamethonium 50 mmol litre^{-1} in mouse (male Swiss-Webster albino) diaphragm preparations (unpublished observations) which closely resemble those in human skeletal muscle and the "small" contracture in porcine skeletal muscle reported by Nelson [1]. We have only observed occasional small (one patient = 0.4 g; two patients = 0.3 g; two patients = 0.2 g) contractures to suxamethonium 50 mmol litre^{-1} in muscle from 97 patients diagnosed as MH susceptible ([3, 4] and unpublished observations). These contractures were similar in magnitude to suxamethonium contractures observed by other investigators [5]. Therefore, we do not believe that a contracture to suxamethonium relates to MH.

The fact that the three patients exhibiting contractures to suxamethonium in the Nelson study were from the same family suggests that this family possesses some abnormality unrelated to the MH defect. This abnormality is not shared by the three MH susceptible patients who were not family members in the same study. We find the observations of Dr Nelson interesting. However, we do not believe that contractures to suxamethonium relate specifically to MH.

J. E. FLETCHER
F. H. LIZZO
H. ROSENBERG
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SIR,—Drs Fletcher, Lizzo and Rosenberg state that they do not believe that *in vitro* muscle contractures to suxamethonium (we observe in MH human and pig muscle) relate specifically to MH. This view is based on interpretation of our data which I believe is incorrect.

Based on their experience of contracture-testing of six pigs compared with our experience with 200, they suggest that a breed difference may explain our results. We did suggest that a genetic, but not a breed, difference may be involved. In fact, we have observed these *in vitro* contractures to suxamethonium in gracilis muscle from MH phenotype H in pure bred Poland China and Pietrain pigs. Thus it is difficult to find substantiation for their statement…"results obtained in the pig cannot relate specifically to MH…" It is interesting that, in their own studies, these authors have observed five of 95 MH positive diagnostic human patients whose muscles also produced *in vitro* contractures to suxamethonium 50 mmol litre^{-1}. If they have observed no suxamethonium contractures among the MH negative patients, their results seem to support our observations.

Finally, Fletcher and colleagues misrepresent our original report by stating "The fact that the three patients exhibiting contractures to suxamethonium in the Nelson study were from the same family suggests that this family possesses some abnormality unrelated to the MH defect." We clearly stated that the suxamethonium contractures were "observed among five MHS human patients with phenotype H diagnosis" and that "the other three MH patients are not related." Our experience is consistent with the view that certain genetically predisposed MHS phenotype H pigs of either the Pietrain or Poland China pure breeds and the occasional phenotype H human will provide muscle that responds abnormally with small contractures to suxamethonium.

T. E. Nelson
Houston

PREDICTING DIFFICULT INTUBATION

Sir,—Wilson and colleagues [1] have made a valuable contribution to the literature on difficult tracheal intubation, in publishing their method of predicting difficulty, and in revealing that obesity can be a factor. Their study confirms our own findings [2] on the contribution made by limitation of head extension, receding mandible and retrognathic position of the lower incisor teeth. We used lateral radiographs to select the best measurements to discriminate between a group of patients in whom tracheal intubation had been particularly difficult, and another group of patients in whom intubation was easy. We then evaluated prospectively a method of assessing this information at the bedside.

We found that the amount of chin in front of the line of vision played an important part, and feature A in their study presumably corresponds very closely to this. However, in their table the authors have not included measurements, standard deviation or *P* value for feature A, and there is some suggestion in the table that feature A could prove to be significant.

We concur that no single factor may be used to predict difficulty. A second and even a third factor in a particular patient may cumulate to result in intubation difficulty where none of the factors separately would have been sufficient. However, we cannot agree that the false positive rate was unacceptably high; a false positive rate of 12% should not be unbearable for a consultant evaluating patients for his own list. Comfortingly, the rate decreases as the Risk-sum criterion increases. The anaesthetist should be on the alert in the case of the emergency patient with a full stomach with a 5% likelihood of being difficult (Risk-sum criterion > 1); he should be on red alert when the risk sum criterion reaches 2 or more (8% likelihood of being difficult), because of the high mortality with failed or delayed intubation in such patients.

Our model [2] has not failed to warn of difficulty in more than 1300 intubations. However, this is only a partial test, as the anaesthetist (C.P.B.) normally uses an angulated laryngoscope, designed to facilitate otherwise difficult intubation. This evidence leads us to suggest that our model, while simpler to use and with a selection of end-points, may have true positive and false positive rates at least as good as the one described by Wilson and colleagues.

Contrary to the conclusion of Wilson and colleagues, we maintain that anaesthetists should be aware that they now have improved and worthwhile ways of predicting which patients are likely to be at risk of difficult intubation. An anaesthetist can respond to the likelihood of difficulty in a particular patient by assembling a range of intubation aids. Further, he can refer potentially difficult patients to a more experienced colleague. A major reduction may then be made, in the developed world, from the 600+ annual deaths from complications at the time of tracheal intubation [2].

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C. Doré
London

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Sir,—We wish to congratulate Dr Bellhouse and Caroline Doré [1] on their excellent study. We are delighted to find that we agree on many points. Unfortunately, we are unable to provide the mean and standard deviation for feature A. We thought that the amount of mandible posterior to the line of sight (B) would be more relevant, therefore we dropped the direct measurement of A to reduce the burden of data collection.

We agree that even tests with disappointing false positive rates may be useful for certain purposes. Whilst agreeing that anaesthetists should realize that there are improved ways of detecting patients at risk, we are anxious to stress that, as no test is likely to be perfect, anaesthetists must be trained to deal with the unexpectedly difficult intubation.

M. E. Wilson
Bath
D. J. Spiegelhalter
Cambridge

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AID TO INTUBATION

Sir,—With reference to the interesting discussion of the use of fibreoptic instruments for difficult intubation in the first Editorial of your January issue, might I suggest the use of a very old aid to intubation?

The use of a bite-block for the oral placement of such a device is obvious; however, the size of tracheal tube possible is then very limited. However, the "divided airway" of 1940's vintage [1] obviates this problem: being designed to direct a thin flexible rubber Magill tube into the larynx, it facilitates the passage of a fibreoptic laryngoscope, and its subsequent removal is easy. We have one in our department museum—it works perfectly. Surely they would be easy to have manufactured?

I claim no priority in suggesting this idea: readers of Sykes' *Essay on the first hundred years of Anaesthesia* will recognize the source.

B. E. WELSH
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THE RECOVERY INTEREST GROUP

Sir,—Day case surgery and endoscopy are increasing. In contrast to inpatients, Day Hospital cases may be impaired less by the therapeutic process than by the rate of recovery from drugs, anaesthetics, analgesics or sedatives used to facilitate the procedure.

There is no simple testing scheme which may be used routinely to determine the existence of residual impairment. At a national workshop held here in Cardiff last summer, it was agreed that the accurate measurement of post-drug impairment is a problem in both clinical practice and research. It was felt that the opportunity to discuss experiences and problems in this field was informative and that there is a need for better communication between those involved in the assessment of functional impairment. We have, therefore, established a **Recovery Interest Group,** with three aims:

(1) To establish and circulate a register of members' research, an annually up-dated list giving details of tests used, currently and in the past, in addition to drugs investigated.

(2) To produce an annual newsletter.

(3) To promote regular workshops to discuss developments and to foster communication.

Further details of the group may be obtained by writing to:

Dr Lalage Sanders,
Recovery Interest Group,
Department of Anaesthetics,
University of Wales College of Medicine,
Heath Park,
Cardiff CF4 4XW.

M. ROSEN
L. SANDERS
Cardiff

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BOOK REVIEWS

An Introduction to Anaesthenology. Edited by A. Coetzee and W. van der Merwe. Published by Oxford University Press. Pp. 520; indexed; illustrated. Price £29.50.

An Introduction to Anaesthesiology is a product of the Department of Anaesthesiology in Stellenbosch University School of Medicine. It is a multi-author text, with 24 contributors, and is intended for "the undergraduate student in medicine as well as the general practitioner." It has some of the disadvantages of a multi-author work, for example repetition and differences in presentation between chapters, but shows the cardinal virtue of expertness, often absent when one or two authors tackle a wide range of subjects.

There is a good deal of physiological background and this generally blends well with the clinical parts of the work. It is reasonably comprehensive, with sections on local analgesia and on resuscitation. The text is easy to read, the illustrations informative, and the style relaxed—sometimes a little too relaxed for lucidity. The clinical teaching it contains is generally acceptable to anaesthetists in the United Kingdom, although there are exceptions.

Anaesthesia does not occupy a large place in the undergraduate curriculum in the United Kingdom. The book is too long and too detailed for any except the very best; undergraduates, as a whole, would do better to confine their attentions to one of the several shorter works available. It would, however, serve as a useful introduction to those starting anaesthesia as a career or practising it for a short time before proceeding to something else. Certainly, as a statement of basic principles, it has a great deal to recommend it.

J. E. Utting

Surgery for Anaesthetists. Edited by J. S. M. Zorab. Published (1988) by Blackwell Scientific Publications. Pp. 512; illustrated; indexed. Price £48.60.

The current interest in anaesthetic safety and monitoring seems to me to miss one thing. A mirror attached to the operating lamp should give the anaesthetist a view of what the surgeon is doing, so that problems may be anticipated or detected early but, if the anaesthetist is to interpret what s/he sees, s/he requires a reasonable knowledge of surgery. This book sets out to fill that possible gap in knowledge. Dr Zorab has inspired pairs of surgeons and anaesthetists to present the essential surgical problems, together with ideas on how they affect anaesthetic management.

The sections of the book cover general, urogenital, plastic and reconstructive, cardiothoracic, vascular, gynaecological, orthopaedic, paediatric, neurological, ophthalmic and ENT surgery. Some are very good indeed, particularly those dealing with the sub-specialties of cardiothoracic, neurological and paediatric surgery These will certainly help candidates for the Part III Fellowship, who may have little experience in these fields. Others are less helpful, possibly because of an excessive amount of surgical technique, as in the sections on gynaecology and urology.

There is one major omission. The section on obstetric and gynaecological surgery makes no mention of any obstetric operation—not even Caesarean section. Yet this is one of the main areas where knowledge of each other's problems would assist the obstetrician and the anaesthetist. A second edition should correct this.

Overall, this is a useful book to which trainees can refer for some basic surgical data which will help to provide better anaesthesia. It will be a useful addition to departmental libraries. Dr Zorab envisages a sequel: *Anaesthesia for Surgeons*. Now that will be an exciting prospect!

J. Norman

Anaesthesia and Co-Existing Disease, 2nd Edn. Edited by R. K. Stoelting, S. F. Dierdorf and R. L. McCammon. Published by Churchill Livingstone Inc., New York. Pp. 936; illustrated; indexed. Price £50.00.

The implications of intercurrent disease on anaesthetic management have been the subject of a number of recent articles and books including this one which now goes into its second edition some 5 years after initial publication. A problem inherent in this type of textbook is the necessity to discuss comprehensively many aspects of diseases which may be encountered in anaesthetic practice and yet at the same time provide useful practical advice on anaesthetic management. To this end, it is the editors' avowed intention that each chapter should provide a brief description of the pathophysiology of a disease state and its medical treatment with relevance to the perioperative period, and then discuss specific anaesthetic management. In general, this aim is achieved, although the degree of detail is occasionally variable and the organisation of some sections of the book could be improved.

An illustration of this unevenness is found in the description of shock. Despite great emphasis on cardiovascular disease (13 chapters; 194 pages), this subject is fragmented into separate sections on hypovolaemic, cardiogenic and septic shock. Septic shock is described in the chapter on infectious disease in a brief and superficial description concentrating on the rather obscure subject of the role of endorphins. Acute renal failure, a most important subject for anaesthetists, is considered under the heading of perioperative oliguria, and here the topics of fluid management, filling pressure and specific therapy could be expanded considerably.

In discussing respiratory disease in anaesthesia, the impact of surgery on pulmonary function is of prime importance, but this subject is confined to the end of the chapter on obstructive airways disease, following description of anaesthetic management. While this is presumably an introduction to the section on postoperative pulmonary complications, it nevertheless is a subject which must be understood before anaesthetizing a patient with pulmonary disease.

The extent of discussion of anaesthetic management varies between subjects. For example, in certain chapters there is a full discussion of the anaesthetic management for surgical treatment of the disease (congenital heart disease, aortic aneurysm, neonatal abnormalities). In other chapters, such as that on valvular heart disease, the discussion of anaesthetic management concentrates only on anaesthesia for non-associated surgery.

In an attempt to be comprehensive, the editors have included chapters on paediatric anaesthesia and obstetric anaesthesia. These describe the anatomy, physiology and pharmacology relevant to these areas and cover briefly the anaesthetic management of conditions such as tracheo-oesophageal fistula, diaphragmatic hernia and pyloric stenosis. Anaesthesia for Caesarean section, both general and regional, is covered in just four pages. It is debatable if these subjects are appropriate in a book devoted primarily to the anaesthetic implications of intercurrent disease.

There are several areas where there is a degree of vagueness; for example, the use of PEEP in chronic obstructive pulmonary disease, prophylaxis against sub-acute bacterial endocarditis, the assertion that volatile agents are not advisable in hypothyroidism, and that cricoarytenoid arthritis is "common" in rheumatoid arthritis.

Overall, this book is very readable. It is well illustrated and there are many useful diagrams. It is well indexed and contains many useful references, although there is an irritating mix of review and original articles.

This book is strongest on the more obscure conditions. It will be particularly useful when one is called upon to anaesthetize a patient with one of those rare eponymous syndromes and urgently requires a concise and practical description of the anaesthetic implications. For this reason, it should find its way on to the shelves of many personal and departmental libraries.

I. S. Grant

Understanding Anaesthesia, 2nd Edn. By L. E. S. Carrie and P. J. Simpson. Published by Heinemann Professional Publishing, London. Pp. 501; indexed; illustrated. Price £25.00.

The authors hope that this second edition will have wide appeal because of its increased scope compared with the first edition. New sections include microvascular surgical anaesthesia, the use of lasers, modern monitoring equipment and the pharmacology of recently introduced drugs.

This is an easy book to read, with bold headings, short paragraphs and short chapters: 48 chapters, averaging 10 pages each. The book is written in an attractive style using a direct, simple approach with a few relevant illustrations.

The only disappointments are the very limited descriptions of regional blocks (lower limb blocks are not mentioned) and some incorrect statements (lignocaine, atropine, diazepam, pancuronium do not trigger MH!). Nevertheless, the authors have clearly tried to encompass the whole of anaesthesia, including such specialist areas as vascular, thoracic and neonatal surgery, endocrinology and relevant general medicine, in addition to covering the more practical aspects of the specialty.

In view of its broadly based approach, it should be a most adequate text for ODAs and nurses intending either to take a course in anaesthesia or to specialize in ICU. I doubt if any book can be suitable for ODAs, nurses *and* medical students, as their requirements are different. The average medical student could be daunted by even the thought of 500 pages of text, although new SHOs would gain a lot by reading it before a more detailed book is attempted.

Unfortunately, *Understanding Anaesthesia* is now too thick and heavy for the pocket of a white coat. As a "table model" it should live in all Departments of Anaesthesia and Medical Libraries. I quickly lost my 1st Edition to the recovery room, where it has entertained and instructed many generations of both trainee and postgraduate nurses.

F. R. Ellis

Neonatal Anaesthesia, 1st Edn. Edited by D. R. Cook and J. H. Marcy. Published by Appleton Davies Inc., Pasadena. Pp. 262; indexed; illustrated. Price £40.00.

The evolution of paediatric anaesthesia as a viable subspecialty in recent years makes it increasingly important for those working in the field to have access to up-to-date information from specialist literature. The aim of this book (editors and authors of which are all from the Children's Hospital of Pittsburgh), is to provide such information on both the theory ("why") and the practice ("how") of neonatal anaesthesia.

Specific differences from the adult in anatomy, physiology and pharmacology are greatest in the neonate, and one of the strengths of this book is that it covers these basic subjects in considerable detail. Persistent pulmonary hypertension of the newborn receives a chapter of its own, as do thermoregulation and fluid therapy, and the chapter on paediatric anaesthetic pharmacology is particularly comprehensive. There is much useful information for the British anaesthetist in these chapters.

When it comes to the more practical aspects of the subject (the "how"), the differences between the North American and British approaches begin to emerge. In the chapter on breathing systems, for example, there is an emphasis on non-rebreathing valves and circle systems which are seldom if ever used in neonatal anaesthesia in the United Kingdom. Extensive reference to the older, classic literature has been encouraged by the editors (although Macintosh's name is mis-spelt), but sometimes seems to have been done at the expense of more recently published work. This policy can also confuse the reader, for example in the case of congenital pyloric stenosis, where Smith's suggestion that tracheal intubation is not always necessary is given as much weight as the opposing view which most people must surely hold. The more widespread use of sophisticated methods of monitoring is seen in the suggested addition of one-way valves to the breathing system to allow use of the mass spectrometer It is encouraging, however, to read that the precordial stethoscope has not been abandoned. It is surprising that central venous cannulation is dismissed as being of limited use in the neonate, and its use is not mentioned in relation to vasodilator therapy in the management of diaphragmatic hernia.

Some of the advice given is impractical, such as increasing the operating theatre temperature to 32 °C, and there is a lack of detail such as drug doses or minimum urine flows. Some of the techniques advocated have been abandoned in the U.K., for example the performance of gastrostomy under local analgesia with a "whisky nipple" for oesophageal atresia, and many would find awake intubation in a paralysed neonate unacceptable. There are several notable omissions, such as neurosurgery, urogenital anomalies, hepatic problems and many of the common intestinal malformations. Hypocalcaemia is mentioned only in the context of resuscitation. More mention could have been made of the congenital anomalies which may be associated with common surgical defects, such as Pierre Robin syndrome. The suggestion that respiratory depression "is very unlikely" in this age group after morphine 0.2 mg kg^{-1} is rather alarming.

Many will find the chapters on neonatal resuscitation and respiratory care useful, and the closing chapter on medical ethics and the neonatal anaesthetist, although written in the framework of American Law, contains messages for us all.

The book is well produced, with clear printing which is easy to read, although illustrations are sparse and there are no radiographs. It does not contain enough detail to allow the reader to anaesthetize a neonate without supervision—which is probably a very good thing—but provides a useful outline of the general principles upon which sound neonatal anaesthesia must be based.

D. J. Hatch

Anaesthesia for Thoracic Procedures. Edited by BE Marshall, DE Longnecker and HB Fairley. Published by Blackwell Scientific Publications Ltd, Oxford. Pp. 632; indexed; illustrated. Price £24.50.

This comprehensive textbook reviews all aspects of anaesthetic management of patients undergoing investigative and operative procedures performed in the thorax.

The anatomy and physiology of the lung are reviewed well and there is a separate chapter dealing with evaluation of lung function, with special reference to patients scheduled to undergo pulmonary resection. Pharmacology is discussed in depth, and there are chapters which describe the preoperative assessment of diseases of the chest wall or mediastinum, and of concurrent medical disease. The psychological preparation of the patient is discussed in detail in a separate chapter.

There is a fascinating description of the development of thoracic anaesthesia. Surgical approaches and positions are discussed and there is an important chapter detailing methods of infection control during anaesthesia and surgery.

The remainder of the book is devoted to descriptions of the anaesthetic management of specific thoracic procedures, including endoscopy and surgery of the lung, trachea, mediastinum and oesophagus. The management of patients who have undergone thoracic trauma is discussed in depth; penetrating wounds appear to be commoner in the United States than in Europe, and the authors note that more than 10000 deaths occur annually in that country as a result of gunshot wounds. The problems related to heart–lung transplantation are addressed; included in this chapter is a section headed enigmatically "Anesthetic care of the donor", but which deals with the perioperative management of the cardiovascular and metabolic disturbances that may occur. Finally, the postoperative management of the patient who has undergone thoracotomy is discussed, and common complications described.

The book represents extremely good value for money. It contains information which will be of benefit both to the trainee and to the experienced thoracic anaesthetist. The editors have, perhaps, attempted to provide too comprehensive a review; the chapters on pharmacology and concurrent medical disease are general in nature, and are superfluous in a book of this type. Many of the chapters are illustrated liberally, although the quality of artwork is variable. However, these are minor quibbles. This is an excellent book which will compete keenly with its rivals on both sides of the Atlantic.

A. R. Aitkenhead

Anatomy for Anaesthetists. Edited by H. Ellis and S. Feldman. Published by Blackwell Scientific Publications, Oxford. Pp. 376 indexed; illustrated. Price £34.50.

This is the fifth edition of a well known book. The clear diagrams (which alone make the book worthwhile) have been retained and the text is easy to read and very clear. The book comprises four parts dealing with the ventilatory pathways, the heart, the vertebral canal and its contents and peripheral nerves, whilst a fifth part deals with zones of anaesthetic interest. This leads to some confusion regarding allocation of contents to each section; for example the brachial plexus is dealt with under peripheral nerves, whereas the first rib appears in the fifth section of the book.

The majority of anaesthetists will be interested in anatomy, particularly when they face the Part III of the Faculty of Anaesthetists examination. As the syllabus of this particular part is extensive, any easing of the burden of preparation by a concise text will be appreciated. Does this book contain adequate information to answer the examination? I checked the anatomy questions in the last six Part III exam papers (that is since the change in format of the written papers, which has decreased the time available to answer each question from 45 to 30 min). In five questions the content of the book would have provided sufficient information to answer the questions adequately, but in the sixth instance the amount of detail was inadequate. This sixth question concerned the anterior spinal artery of the spinal cord, surely an area of anatomy of considerable interest to any anaesthetist who is involved in thoracic aneurysms, coarctations and orthopaedic operations for straightening the thoracic vertebrae (it has been described in an anaesthetic review of thoracic aneurysms).

Currently, there are many textbooks on regional analgesia dealing adequately with relevant anatomy and (as mentioned in the introduction) the authors have aimed not to duplicate such information.

Aspects of embryology are discussed, although this review was surprised at some of the topics chosen. For example, there is a picture of the derivatives of the branchial arches, which I sincerely hope none of my co-examiners would seek to examine, even if they were conversant with this subject! However, there is no discussion of the problems of the division of the truncus arteriosus which can lead to Fallot's tetralogy and, in the extreme form where there is no spiral twist, to transposition of the great arteries. Incidentally, there is no mention of transposition of the great arteries in the description of congenital abnormalities of the heart, although this lesion is almost as common as Fallot's tetralogy.

Every department of anaesthesia should possess a copy of this book, but I doubt the necessity for individual candidates to own a copy.

J. B. Bowes

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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

HIGH FREQUENCY VENTILATION

High frequency ventilation has been described as "a physiological curiosity looking for a clinical application." It is now 20 years since the technique was first used to minimize the cyclical effects of ventilation on arterial pressure [1] and it is appropriate, therefore, to consider if high frequency ventilation has made any major impact on clinical practice and if further research is likely to produce any useful results.

The basic aim of high frequency ventilation is to secure adequate gas exchange with small tidal volumes in the hope that this will minimize peak airway pressures and so reduce the incidence of pulmonary barotrauma in patients with severe acute lung disease. Although many different devices have been used, current interest is centred on four main techniques: high frequency positive pressure ventilation (HFPPV); high frequency jet ventilation (HFJV); high frequency oscillation (HFO); and high frequency chest wall oscillation (HFCWO).

The ventilator system used in the early HFPPV experiments used a high pressure gas source and a solenoid valve to deliver pulses of gas to an insufflation catheter placed within the tracheal tube. Expiration was passive and controlled by a variable resistance. With this system, which had minimal internal compliance and deadspace, it was found that peak pressures at 60 b.p.m. were approximately 65% of those generated at 20 b.p.m. However, the deadspace:tidal volume ratio increased as tidal volume was reduced, so that large ventilation volumes were required to maintain normal arterial blood-gas tensions at the higher frequencies. Furthermore, increases in lung volume occurred if the inspiratory time was greater than 33% of the total cycle time. In later ventilators the expiratory resistance was replaced by a pneumatic valve system [2] and ventilation nomograms were developed to facilitate the application of the technique during anaesthesia for bronchoscopy and laryngoscopy [3].

Studies of gas exchange in dogs [4] and humans [5] have shown that there is a reduction in the effective deadspace as tidal volume is reduced up to frequencies of 60 or 80 b.p.m., but thereafter there is a linear increase in ventilation volume requirement with increasing frequency so that volumes of 20–30 litre min^{-1} may be required at 200 b.p.m. As the frequency is increased, the expiratory time is decreased so that the end-expiratory lung volume is increased. This results in an increase in mean intrathoracic pressure and a reduction in cardiac output. The increase in lung volume and the increased flow rates required to produce the high ventilation volumes result in an increase in peak airway pressures, so little seems to be gained by ventilating the lungs at frequencies in excess of 80 b.p.m.

In HFJV, pulses of gas are delivered at high velocity through an orifice place in a T-piece connected to the tracheal tube or through a narrow tube incorporated in the wall of a special tracheal tube. The jet entrains gas from the T-piece or open end of the tracheal tube during the early part of inspiration, but entrainment ceases and spillage occurs when the airway pressure increases towards the end of inspiration. As the kinetic energy of the jet is converted to potential energy in the trachea, it develops a normal flow profile so that the physiology of gas exchange at frequencies up to 120 b.p.m. appears to differ little from HFPPV. However, a jet ventilator is essentially a pressure generator, so that tidal volume is dependent on the impedance of the respiratory system. Because of the high velocities of gas flow required to produce the large ventilation volumes at high frequencies, changes in airway resistance have a marked effect on tidal volume. Conversely, as the elastic recoil pressure is small at low tidal volumes, changes in compliance have relatively little effect on the degree of entrainment or spillage. The major advantage of HFJV is the flexibility of the patient interface resulting from the small diameter of the jet tube. It may therefore be used to provide ventilation when it is not possible to obtain an airtight seal between the ventilator and bronchus (e.g. in surgery of the open bronchus or trachea) and it greatly facilitates surgery when access is restricted (e.g. laryngeal surgery). Cricothyroid injection is of great value during difficult tracheal intubation, but in all these circumstances it is vital to maintain a clear expiratory pathway to obviate over-distension of the lung.

One of the major disadvantages of HFJV is that it is difficult to measure tidal volume. The adequacy of ventilation must be assessed, therefore, by measurement of the end-tidal carbon dioxide concentration during interpolated large breaths [6] or by analysis of an arterial sample. The development of a method of continuous measurement of tidal volume during HFJV may help to minimize the hazards resulting from the rapid variations in tidal volume during the use of this technique [7]. Although there is extensive clinical experience with HFJV and although it has practical advantages in the situations already mentioned, treatment with HFJV does not appear to improve mortality in ARDS [8] or in patients with a bronchopleural fistula [9].

What, then, of high frequency oscillation? This technique was originated by Lunkenheimer [10]. It differs from the other techniques in that expiration is assisted actively, a sinusoidal pattern of oscillation being provided by a piston or loud speaker system at frequencies varying from 5 to 50 Hz. A bias flow of fresh gas crosses the oscillating gas flow to bring in oxygen and remove carbon dioxide; the expiratory limb of this bias flow system consists usually of a long narrow tube which provides a relatively low resistance to the steady bias flow, but a high impedance to the high frequency oscillations.

As the stroke volume of the oscillator is 40–70 ml (less than the volume of the conducting airways) and yet arterial $P\text{CO}_2$ can be maintained within normal limits, there has been intense interest in possible mechanisms of gas exchange [11]. However, there is still little agreement on the relative importance of each mechanism, for it is probable that this varies with species, frequency of oscillation and the geometry of the airways and oscillator system used. The situation is rendered more complex by the recent demonstration that the volume of gas entering the lungs may be greater than the stroke volume of the pump, because of resonant amplification. Furthermore, there may be regional differences in the distribution of ventilation, which may vary in a cyclical fashion as different zones move in and out of resonance [12, 13]. There is a need for much further study of these mechanisms.

The greatest clinical interest in HFO is in the neonatal field, where alveolar collapse results from surfactant deficiency. In the neonatal respiratory distress syndrome, the inspiratory limb of the pressure–volume curve displays an inflection point which is convex towards the pressure axis at the point where alveolar units re-expand. The expiratory limb of the curve shows marked hysteresis so that the lung volume at any given inflation pressure is much larger during expiration than during inspiration. It has been suggested that a sustained inflation followed by HFO enables the lung to be maintained on the expiratory limb of the pressure–volume curve, with maintenance of lung expansion and improved gas exchange. In the lung lavage model of the neonatal respiratory distress syndrome, Bryan's group in Toronto has shown that HFO results in a marked reduction in hyaline membrane formation compared with conventional mechanical ventilation at the same mean airway pressure [14]. Other studies in a similar preparation suggest that the important factor in preventing hyaline membrane formation is not the high frequency but the maintenance of lung volume above the inflection point on the pressure–volume curve [15]. Further work from the Toronto group has suggested that hyaline membrane formation is associated with the presence of intra-regional stresses, because of repeated opening and closing of alveoli, and that these stresses activate polymorphonuclear granulocytes which in turn increase capillary permeability [16].

HFO has now been used, with success, in the treatment of the neonatal respiratory distress syndrome [17]. However, a recent N.I.H. trial carried out in 11 North American centres has failed to show any convincing advantage of HFO when compared with conventional treatment. As many of the centres involved in the study had little previous experience with the technique, and as there were a number of other serious objections to the design of the trial, there are strong grounds for believing that such a trial should be repeated in Europe.

The fourth technique of interest, HFCWO, has been shown to be capable of maintaining adequate gas exchange in small animals, but appears less suitable for use in humans because of the high power required to produce adequate oscillations of the chest wall and because of the discomfort of the procedure. However, studies in patients with chronic obstructive pulmonary disease using HFCWO at 5 Hz showed that gas exchange was improved and the spontaneous frequency of breathing was decreased [18]. Whilst the physiological effects appeared to be relatively small, it is possible that further developments in this field may prove of use in stimulating gas exchange during episodes of acute respiratory failure.

It is apparent that there are many ways of sustaining gas exchange which are outside the bounds of conventional physiology, and there is a potential for manipulating the lung and preventing lung damage which needs further exploration. Whether or not high frequency ventilation is integrated into clinical practice, it has certainly extended the frontiers of respiratory physiology.

M. K. Sykes

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IN VITRO INVESTIGATION OF THE PRIMING PRINCIPLE FOR RAPID NEUROMUSCULAR BLOCK

R. J. STORELLA, J. JAFFE, E. MEHR AND H. ROSENBERG

SUMMARY

The priming principle was investigated in the rat phrenic nerve–diaphragm preparation stimulated continuously at 0.2 Hz. Tubocurarine was added to the organ bath as either a single (non-primed) or a divided (primed) dose. Priming consisted of 15% or 20% of the final dose, with priming intervals of 5 or 10 min. Priming decreased significantly the time to 80% block and was associated with mild neuromuscular block. A simple model adequately predicted the time to 50% and 80% block, using the same diffusion constant for both primed and non-primed conditions. The onset of neuromuscular block, with and without priming, depended mostly upon the distribution of the drug to its site(s) of action.

The "priming principle" is used to hasten non-depolarizing neuromuscular block and facilitate intubation of the trachea by administering the drug in divided doses [1, 2]. A small fraction (10–15%) of the final dose of the drug, which should not cause significant weakness, is administered. Subsequently, after a priming interval (e.g. 3–5 min), the remainder of the blocker is administered. Several clinical reports have confirmed the effectiveness of the priming principle [3–7].

Although there is general agreement that priming can decrease the time to intubation, some investigators [8–11] have expressed concern regarding the safety of priming, suggesting that priming shortens intubation time only under conditions that compromise ventilation.

Schwarz and colleagues [2] suggested that priming decreases the margin of safety. Although this is commonly assumed to be the mechanism for priming [12], it has not been demonstrated in a quantitative manner. Black and colleagues [3] reported that the priming effect did not increase with the priming dose, a result which is not consistent with the mechanism of action proposed by Schwarz [2]. The involvement of prejunctional acetylcholine receptors also has been suggested [3, 5, 13, 14]. Thus the relative importance of the magnitude of the priming dose and the duration of the priming interval is uncertain [6, 11, 13, 15, 16].

The present *in vitro* study was designed to study these factors.

MATERIALS AND METHODS

Male Sprague–Dawley rats were killed humanely and the left phrenic nerve–hemidiaphragm dissected and removed. The tissue was bathed in physiological saline solution (a modified Krebs containing (mmol litre^{-1}): NaCl 118; $NaHCO_3$ 25; KCl 3.3; KH_2PO_4 1.1; $CaCl_2$ 2.5; $MgCl_2$ 0.9; glucose 11.1; choline chloride 0.01; pH = 7.4 at 37 °C) and aerated with carbon dioxide in oxygen. The left hemidiaphragm was cut into a strip approximately 5 mm wide, with the phrenic nerve inserting at its middle. Surgical silk suture (4–0) was tied around a small fragment of ribs and fixed to a post in the middle of a glass organ bath maintained at 37 °C containing 30 ml of physiological saline. The central tendon was ligated and connected to an isometric tension transducer (Grass FT-03). The phrenic nerve was ligated and drawn through a circular bipolar stimulating electrode which was suspended in the saline. The length of the preparation was adjusted to yield

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maximum tension to supramaximal stimulation of the phrenic nerve at 0.2 Hz (0.2-ms square wave).

After equilibration, tubocurarine was added in volumes of less than 200 μl. The drug treatment was divided into two periods. In the first period, a "priming dose" of 15 or 20% of the total dose, or no drug, was added. After a priming interval of 5 or 10 min, the remainder of the dose or the total dose was given. The final drug concentrations were approximately two or three times the ED_{95}.

Neuromuscular block was measured as the percent decrease in twitch tension from that immediately preceding the first period. The times to 50 and 80% block of contractile tension (T_{50} and T_{80}) were measured from the beginning of the second period. One experiment was performed on each phrenic nerve–diaphragm preparation.

We examined the hypothesis that the onset of neuromuscular block, with and without priming, could be described by an application of Fick's law of diffusion. Rats were assigned randomly to one of six groups of eight animals. One group received tubocurarine in various concentrations, in order to determine a steady state concentration–response relationship. Both T_{50} and T_{80} were measured in the other five experimental groups to which tubocurarine was given. Three groups with a final concentration of 4.5 μmol litre^{-1} were primed as follows: 20% for 5 min, 15% for 10 min and 20% for 10 min. Two groups were not primed (final concentration tubocurarine 4.5 and 3.0 μmol litre^{-1}). A typical recording of a primed preparation is shown in figure 1.

To test the diffusion hypothesis, we used the equation $C = A-(A-C_0)e^{-kt}$, where C = concentration of drug at its site of action; A = drug concentration in bath; C_0 = initial concentration at site of action; k = diffusion constant; and t = time. C was related to percent block by a dose–response relationship determined from stable degrees of block from single (non-primed) doses. k was calculated from non-primed ($C_0 = 0$) preparations given tubocurarine 3.0 μmol litre^{-1} and used in making predictions for the other groups. When predicting the onset of block following the administration of the second dose, C_0 was estimated by calculating C at the end of the priming interval, using the Fick equation above.

Results are reported as mean (SEM). Comparisons were made by one-way analyses of variance followed by Dunnett's test, with $P < 0.05$ regarded as significant.

RESULTS

The percent block produced by tubocurarine was determined for eight concentrations at steady state. The relationship between block and concentration was: % block = $(130 \cdot \log C) + 73$ (r = 0.94). The calculated ED_{95} was approximately 1.5 μmol litre^{-1}. In all preparations, tubocurarine both 3 and 4.5 μmol litre^{-1} produced 100% neuromuscular block. The diffusion constant (k) for tubocurarine was derived by solving the Fick equation for k using both the mean T_{50} and the mean T_{80} for tubocurarine 3.0 μmol litre^{-1} and averaging the two values. This mean k (k = 0.00086) was used to predict T_{50} and T_{80} for all tubocurarine-treated groups.

Priming significantly decreased onset time, as measured by T_{50} and T_{80} (tables I, II). The Fick model adequately predicted the onset of neuromuscular block. Table I shows that four of five predictions of T_{50} were within 10% and 1 SEM of observed means. The least accurate prediction was within 20% and the 95% confidence interval

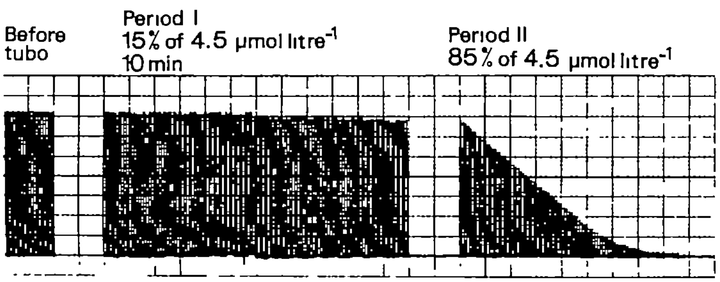

FIG. 1. Typical recording of isometric tension in a phrenic nerve–diaphragm preparation stimulated supramaximally at 0.2 Hz. A priming dose of 15% of the quantity of tubocurarine (tubo.) required for a final concentration of 4.5 μmol litre^{-1} was given at the start of period I and the balance given after a 10-min priming interval. The recording periods are separated on the trace for clarity.

TABLE I. *Observed (mean (SEM)) and predicted times to 50% block for differing final concentration of tubocurarine, both primed and unprimed*

Final concn of tubocurarine (μmol litre^{-1})	Time to 50% block Observed (s)	 Predicted (s)	 Difference from observed (%)
3.0			
No prime	312 (38)	293	6.1
4.5			
No prime	226 (19)	187	17.0
Primed			
20%, 5 min	137 (22)	133	2.9
15%, 10 min	119 (20)	115	3.4
20%, 10 min	95 (8.2)	90	5.2

TABLE II. *Observed (mean (SEM)) and predicted times to 80% block for differing final concentration of tubocurarine, both primed and unprimed*

Final concn of tubocurarine (μmol litre^{-1})	Time to 80% block Observed (s)	 Predicted (s)	 Difference from observed (%)
3.0			
No prime	504 (66)	531	5.4
4.5			
No prime	356 (28)	326	8.4
Primed			
20%, 5 min	266 (39)	272	2.2
15%, 10 min	232 (35)	253	9.1
20%, 10 min	213 (20)	228	7.0

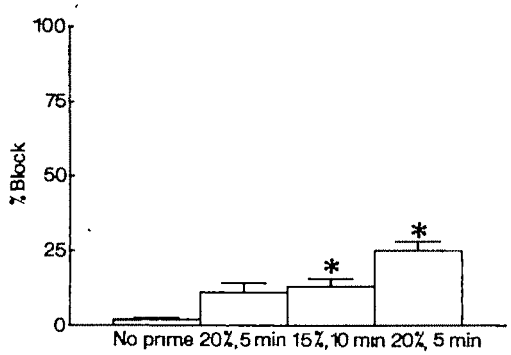

FIG. 2 Degree of neuromuscular block induced by varying priming doses and intervals for tubocurarine (mean (SEM) for eight observations). * $P < 0.05$.

of the observed mean. Similarly, all the predicted T_{80} values were within 10% and 1 SEM of observed means (table II). There was a small degree of neuromuscular block at the end of the priming period (fig. 2).

DISCUSSION

Our data showed that priming accelerated the rate of onset of neuromuscular block in an *in vitro* rat preparation. Significant decreases in onset time were associated with a small degree of neuromuscular block produced by the priming dose, as has been demonstrated also in preliminary studies using vecuronium [17].

A simple model, based on Fick's law of diffusion, adequately described the onset of neuromuscular block (tables I, II) both with and without priming. Thus priming did not appear to change the effect of tubocurarine at its site(s) of action. These results are consistent with the hypothesis that the priming principle is a pharmacokinetic principle, and depends mostly on the distribution of a blocking drug to the neuromuscular junction. Although our results cannot exclude the possibility that prejunctional receptors are involved in acceleration of neuromuscular block produced by priming [3, 5, 6], the priming principle is explained reasonably well without recourse to such considerations.

The model of the priming principle has predictive value (fig. 3). It indicates that an effective way of increasing the rate of neuromuscular block is by increasing drug concentration. It predicts further that the rate constant for the onset of neuromuscular block is not affected by priming. Thus the time to peak drug concentration (and thus the maximum block) is not changed by priming. Rather, the time to a given degree of neuromuscular block is decreased by priming. This may not be obvious if muscle force is measured, as transmission as determined from endplate potentials may be reduced beyond that which results in 100% block of induced twitch [18].

The model also indicates (fig. 3) how the effectiveness of priming is related to C_0, the concentration of drug achieved at the neuromuscular junction at the end of the priming interval. It appears that small changes in C_0 do not greatly decrease the time to 100% block of induced twitch. Thus changes in priming dose or interval which do not have a significant effect on C_0 are not likely to change substantially the time to 100% block.

The clinical situation differs from our *in vitro* system in several respects. The drug is distributed to more compartments *in vivo* and is eliminated. The neuromuscular blocking drug may interact with a variety of other drugs used in the clinical setting and there are species differences in sensitivities to neuromuscular blocking drugs [19]. Thus the *in vitro* model may not completely equate with the clinical setting.

However, the model accords with several clinical studies and permits generalizations. Small increases in priming doses did not substantially increase the effectiveness of priming in clinical studies [6,15]. The model indicates that the decreased onset time of small increases in priming dose or interval would be small and would be obscured by the variable responsiveness of nerve–muscle systems to non-depolarizing blocking drugs in clinical settings [20]. Donati and colleagues [21] came to a similar conclusion using a model of human neuromuscular block.

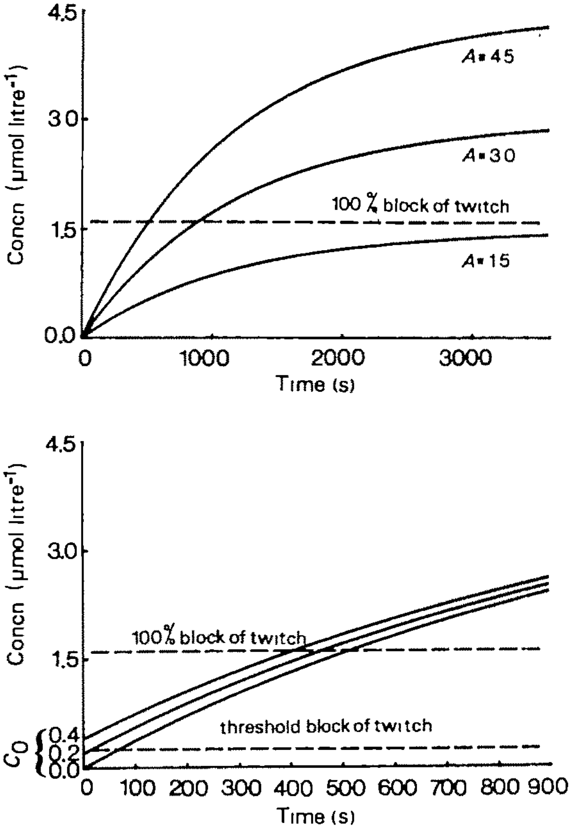

FIG. 3. Top: Predicted effect of increasing the administered concentration of tubocurarine (A) on the concentration at the receptors and the onset time for 100% block of induced twitch without priming. Bottom. Predicted effect of increasing the priming dose on the concentration of tubocurarine at the receptors and the onset time for threshold and 100% block of induced twitch.

We conclude that it is unlikely that any combination of priming dose and duration of priming interval can be found that substantially reduces weakness, and thus respiratory impairment, while retaining an appreciably accelerated onset of complete block. However, techniques that potentiate the block when the induction dose is administered (for example synergistic combinations of non-depolarizing blocking drugs [21]) would be expected to improve the priming principle.

ACKNOWLEDGEMENTS

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ANTAGONISM OF MODERATE DEGREES OF VECURONIUM-INDUCED NEUROMUSCULAR BLOCK BY SMALL DOSES OF NEOSTIGMINE

R. A. JOHNSON AND N. J. N. HARPER

SUMMARY

We have studied the influence of a reduced dose of neostigmine on recovery from vecuronium-induced neuromuscular block in 26 adult patients, using electromyographic responses to train-of-four (TOF) stimulation. Neostigmine 10, 20 or 40 µg kg^{-1} was administered when the first response had recovered spontaneously to 5–10% or 40–50% of control. Antagonism was accepted as adequate when the first response reached 90% of control and the TOF ratio reached 0.7. At both degrees of spontaneous recovery, neostigmine 40 µg kg^{-1} evoked the most rapid antagonism. Clinical recovery was satisfactory with no differences between groups. Block produced by neostigmine was not observed. The pattern of recovery of the single response and the TOF ratio was not altered by neostigmine in the range of doses studied. We suggest that the dose of neostigmine should not be reduced below 40 µg kg^{-1}, even when all responses of the TOF are present.

Neostigmine is used widely to antagonize non-depolarizing neuromuscular block. In the presence of at least 5% recovery of the single twitch, a dose of 2.5–5 mg has been found adequate for all currently used neuromuscular blocking agents, including vecuronium [1–4]. The main characteristics of this drug are a short duration of action and rapid spontaneous recovery [1, 5–7]. Antagonism is more rapid after pronounced spontaneous recovery has occurred [4, 8] and it has been suggested that a smaller dose of neostigmine might be adequate [9] or that it might be omitted [10]. The use of a smaller dose of neostigmine might reduce the incidence of side effects [11].

Antagonists of neuromuscular blockade have differential effects on the recovery of train-of-four (TOF) fade and on the single response [12–14]. Dose-dependent differences in receptor affinity may influence the TOF ratio. In addition to investigating the recovery of the first response of the TOF, we have also studied the effect of small doses of neostigmine on the TOF ratio.

PATIENTS AND METHODS

We studied 26 patients undergoing gynaecological surgery after Ethics Committee approval and after informed written consent was given by each patient. They were allocated randomly to six groups (A–F) according to the dose of neostigmine to be given. Patients of ASA grades III–V and those suffering from neuromuscular disease were excluded.

Monitoring of neuromuscular function

Control values were established for clinical measures of muscle strength before induction of anaesthesia. In the postoperative period the ability to lift the head clear of the pillow for 5 s and the presence or absence of diplopia were noted. Grip strength was measured by recording the pressure generated in a 50-ml syringe containing 15 ml of air by adduction of the thumb against the plunger. Extraocular muscle weakness was assessed with the Maddox Wing [15].

The ulnar nerve was stimulated supramaximally at the wrist via silver–silver chloride electrodes with a TOF impulses of 0.2 ms dura-

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tion at 2 Hz every 20 s. A Relaxograph (Datex) was used to measure and record the integrated evoked compound electromyogram (ECAP) using similar electrodes placed over the adductor pollicis. The ratios of the first ECAP response to the control (T1 : T0) and the fourth response to the first in the same train (T4 : T1) were recorded.

Anaesthesia and antagonism of neuromuscular block

One hour after premedication with diazepam 10 mg and droperidol 5 mg by mouth, anaesthesia was induced with fentanyl 2–3 μg kg^{-1} and thiopentone 3–5 mg kg^{-1}. Anaesthesia was maintained with 70 % nitrous oxide and 0.5–2 % enflurane in oxygen. Ventilation was controlled to produce normocapnia. The control neuromuscular response was recorded and vecuronium 80 μg kg^{-1} given as a bolus. A continuous infusion of vecuronium via a separate cannula was used to maintain 90–95 % depression of the single response. Normothermia was maintained and arterial pressure and ECG were monitored.

Residual neuromuscular block was antagonized at the completion of surgery. Atropine was given in a dose of 0.4 mg per 1 mg of neostigmine. In groups A, B and C the degree of spontaneous recovery was noted (T1 : T0 = 0.05–0.1), the vecuronium infusion discontinued and the antagonist given immediately (10, 20 or 40 μg kg^{-1}, respectively). In groups D, E and F spontaneous recovery was allowed to proceed until T1 : T0 = 0.4–0.5, at which point the antagonist was given (10, 20 or 40 μg kg^{-1}). Recovery of neuromuscular function was regarded as adequate when T1 : T0 and T4 : T1 were consistently greater than 0.9 and 0.7, respectively, at which time anaesthesia and monitoring were discontinued. Supplementary neostigmine 40 μg kg^{-1} was administered if recovery was inadequate after 15 min. Patients were observed in a recovery area for 2 h after operation, and residual neuromuscular block was assessed clinically 30, 60 and 120 min after TOF recovery.

Differences in patient characteristics were assessed with Student's *t* test. The recovery time data were skewed positively and logarithmic transformation was performed. The statistical significance of differences in recovery time between groups was assessed with Wilcoxon's ranked sum test. $P < 0.05$ was accepted as being significant.

RESULTS

There was no difference between the groups with regard to age, weight or total dose of vecuronium. The degree of spontaneous recovery at which neostigmine was given was within the specified range in groups A–C and D–F (table I).

All patients, including those who needed a supplementary dose of neostigmine, fulfilled our criteria of satisfactory neuromuscular function at the end of the study. There was no clinical evidence of weakness in any patient after the return of consciousness.

Antagonism at minimal spontaneous recovery

When antagonism was attempted at the greater degree of block (T1 : T0 = 0.05–0.1, one or two twitches of the TOF present) recovery to T1 : T0 = 0.9 was more rapid in group C (the highest dose of neostigmine) than in groups A ($P < 0.01$) or B ($P < 0.05$) (fig. 1). Recovery of T4 : T1 to 0.7 was also more rapid in group C than in the other groups ($P < 0.05$) (fig. 2).

Antagonism when moderate spontaneous recovery had occurred

A similar pattern was observed when neostigmine was administered after a greater degree of spontaneous recovery was permitted (T1 : T0 = 0.4–0.5). All patients exhibited four responses

TABLE I. *Patient characteristics (mean (SD))*

Group	*n*	Age (yr)	Weight (kg)	Total vecuronium dose (μg kg^{-1})	T1 : T0 at antagonism (%)
A	5	33.5 (6.2)	57.6 (12.9)	125 (44)	7.8 (0.8)
B	3	36.0 (5.0)	67.0 (16.5)	194 (55)	9.3 (1.5)
C	5	35.0 (2.6)	54.2 (3.8)	160 (30)	9.4 (2.3)
D	5	44.5 (17.0)	58.6 (7.6)	116 (48)	46.6 (2.2)
E	4	42.0 (10.6)	64.8 (9.0)	164 (79)	46.3 (3.1)
F	4	39.3 (12.0)	67.0 (7.6)	146 (46)	44.0 (1.8)

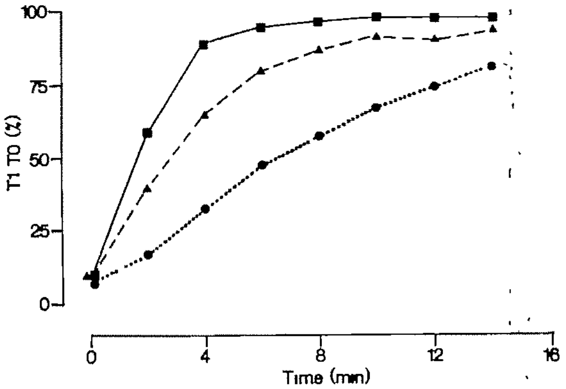

FIG. 1 Mean T1:T0 after administration of neostigmine 10 μg kg⁻¹ (●), 20 μg kg⁻¹ (▲) and 40 μg kg⁻¹ (■) in patients with a minimal degree of spontaneous recovery from vecuronium-induced neuromuscular block.

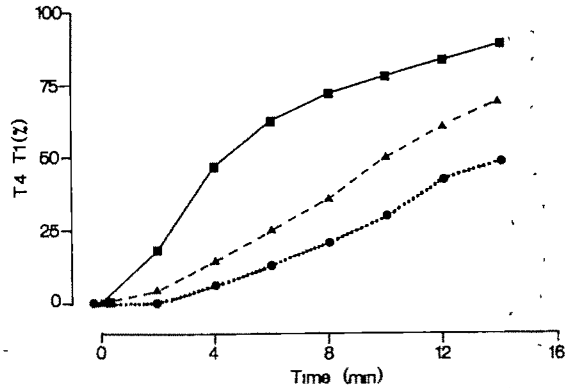

FIG. 2. Mean T4:T1 after administration of neostigmine 10 μg kg⁻¹ (●), 20 μg kg⁻¹ (▲) and 40 μg kg⁻¹ (■) in patients with a minimal degree of spontaneous recovery from vecuronium-induced neuromuscular block.

to the TOF before antagonism. Recovery of T1 was more rapid following the largest dose of neostigmine than in group D who received only 10 μg kg⁻¹ (fig. 3). ($P < 0.05$). The TOF responses recovered more rapidly in group F (40 μg kg⁻¹) than each of the other groups ($P < 0.05$) (fig. 4).

Irrespective of the dose of neostigmine, recovery of both T1 and TOF was more rapid when there had been greater spontaneous recovery ($P < 0.05$), except in comparison of groups B and E where the number of patients was small. There was no evidence of retarded recovery because of "neostigmine block", even when the largest dose of neostigmine was given at a moderate degree of spontaneous recovery.

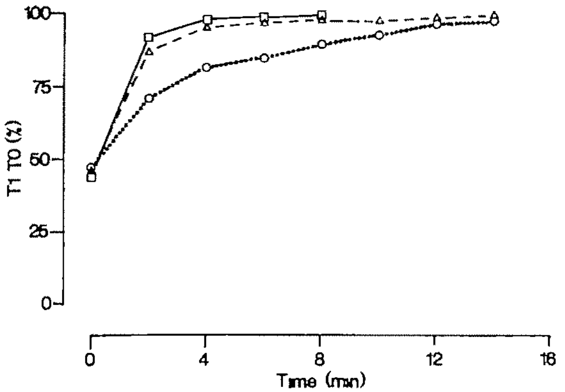

FIG 3. Mean T1:T0 after administration of neostigmine 10 μg kg⁻¹ (○), 20 μg kg⁻¹ (△) and 40 μg kg⁻¹ (□) in patients with a moderate degree of spontaneous recovery from vecuronium-induced neuromuscular block.

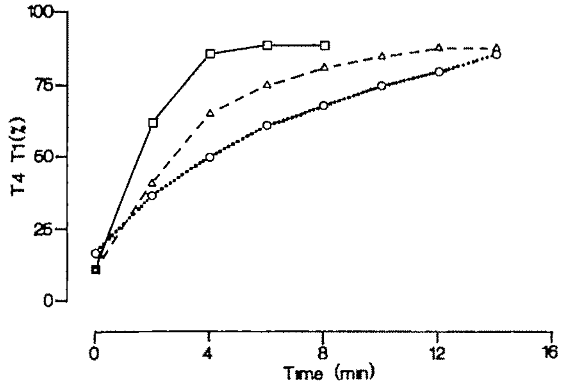

FIG. 4. Mean T4:T1 after administration of neostigmine 10 μg kg⁻¹ (○), 20 μg kg⁻¹ (△) and 40 μg kg⁻¹ (□) in patients with a moderate degree of spontaneous recovery from vecuronium-induced neuromuscular block.

Additional neostigmine

Antagonism of neuromuscular blockade was inadequate in four patients in group A and one patient in each of groups B and D after a single dose of neostigmine. Additional neostigmine 40 μg kg⁻¹ accelerated recovery in all patients and the subsequent rate of recovery was similar to that found after a single dose of 40 μg kg⁻¹ (group F).

Patterns of T1 and TOF recovery

There was no evidence of different patterns of TOF recovery after the different doses of neostigmine, irrespective of the degree of recovery at which it was administered.

Clinical assessment of recovery

Twenty-five of the 26 patients were able to co-operate with the clinical assessments. All 25 could maintain a 5-s headlift. Two patients (from groups B and C) experienced diplopia early in the recovery period.

Twenty-three patients were able to perform the grip strength test. In all groups there was a reduction in strength of up to 20% at 30, 60 and 120 min after recovery of the TOF ratio to 0.7. There was marked individual variation and we were unable to demonstrate a significant change in strength with time, or a significant difference between the groups.

Only 11 patients were able to perform the Maddox Wing test after anaesthesia. Exophoria (ocular divergence) of up to 16 dioptres was found. We did not find differences with time or between groups.

DISCUSSION

This study was intended to simulate closely the clinical situation. We used an anaesthetic vapour to obviate awareness and chose enflurane because many of our patients had previously undergone anaesthesia, notwithstanding its well-recognized potentiating effect on non-depolarizing blocking drugs [16].

The rate of recovery from neuromuscular block may be influenced by the mode of administration of the agent. The spontaneous recovery index (time from T1:T0 = 0.25 to T1:T0 = 0.75) is longer after an infusion of vecuronium compared with administration of the same total dose as a series of boluses [17]. It is, therefore, possible that evoked recovery would be more rapid after bolus administration of vecuronium. In order to achieve a steady plasma concentration, vecuronium was given by continuous infusion. Maintenance of T1:T0 at 40–50% of control throughout the surgical procedure was considered to be inappropriate on clinical grounds. Therefore, in groups D–F neostigmine was given when this level of recovery had occurred spontaneously from the steady state of 90–95% block.

Recovery may be influenced by the total dose of myoneural blocker given during the surgical procedure [2, 17]. Our findings may not be applicable directly when larger total doses are given over a prolonged period.

TOF measurements were supplemented by clinical assessments of recovery for two reasons. First, a small dose of neostigmine exhibits a shorter duration of action than conventional doses [18, 19] and there may have been a risk of recurarization. This could not be excluded by electromyography because supramaximal nerve stimulation in the awake patient is painful. Second, a comparison of the different clinical measurements of residual block was thought to be useful. We were unable to demonstrate significant differences in clinical recovery between the groups, in contrast to previous studies in which residual block persisted for several hours [15, 20].

Recovery from the greater degree of block was slow, even when neostigmine 40 μg kg^{-1} had been given. Smaller doses of neostigmine produced much slower antagonism. In group A (10 μg kg^{-1}) the mean rate of recovery was no faster than that reported during spontaneous recovery [7], and we suggest that these small doses are inadequate. Recovery was also slow after neostigmine 10 μg kg^{-1} when a moderate degree of spontaneous recovery had occurred (group D), and one patient required supplementary neostigmine.

The differences in mean recovery times after neostigmine 20 and 40 μg kg^{-1} were comparatively small. However, there was considerably more variation in the recovery time in the group given 20 μg kg^{-1} and we therefore estimated the time by which 95% of patients would be expected to have reached an adequate level of recovery (ERT$_{95}$)

TABLE II *Times by which 95% of the population sampled would be expected to satisfy the criteria of antagonism (T1.T0 = 0.9 and T4.T1 = 0.7) calculated from the distribution of times to recovery of individual patients. estimated recovery time for 95% (ERT$_{95}$)*

Group	Mean T1.T0 at antagonism (%)	Dose of neostigmine (μg kg^{-1})	ERT$_{95}$ (min)	
			T1.T0	T4.T1
C	9	40	6.2	14.2
E	46	20	10.3	13.7
F	44	40	3.9	3.4

(table II). This approach is analogous to the concept of ED_{95} in relation to drug doses. We suggest that the use of ERT_{95} may be more relevant to patient management than consideration of mean recovery time in isolation.

There was no electromyographic or clinical evidence that the largest dose of neostigmine (40 $\mu g\ kg^{-1}$) produced slower recovery because of "neostigmine block", regardless of whether it was given as a single dose or as a supplement. This finding is not surprising: Payne and colleagues found that neostigmine 2.5 mg produced neuromuscular block only in those patients who had not received a neuromuscular blocking agent [21].

The pattern of train-of-four recovery in this study was similar to that found previously during spontaneous recovery from vecuronium [22]. This suggests that neostigmine does not exert a predominant influence on either pre- or post-junctional receptors [23].

We conclude that evoked recovery from vecuronium-induced block was most rapid after neostigmine 40 $\mu g\ kg^{-1}$ at both minimal and moderate degrees of spontaneous recovery. Recovery was prolonged when the dose was reduced, and the omission of neostigmine would clearly be unsatisfactory. The dose of neostigmine should not be reduced to less than 40 $\mu g\ kg^{-1}$, even when the single response had recovered to 50% of control and there are four responses to TOF stimulation.

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COMPARISON OF MIVACURIUM AND SUXAMETHONIUM ADMINISTERED BY BOLUS AND INFUSION

B. W. BRANDOM, S. K. WOELFEL, D. RYAN COOK, S. WEBER, D. M. POWERS AND J. N. WEAKLY

Mivacurium chloride (BW B1090U), a new short-acting non-depolarizing neuromuscular blocking drug, has undergone initial clinical trials to evaluate its neuromuscular and cardiovascular effects [1–7]. Mivacurium is metabolized by pseudocholinesterase at a rate 70% of that of suxamethonium [8]. Because of its relatively short duration of action, mivacurium may be useful as a bolus to facilitate tracheal intubation and as an infusion to maintain extended neuromuscular block. This study of healthy adult patients undergoing surgery was designed to compare the onset of neuromuscular block and the ease of tracheal intubation after near equipotent bolus doses of mivacurium or suxamethonium, to define the infusion requirements and recovery pattern following cessation of mivacurium or suxamethonium infusion, and to test the predictive value of the time to recovery of 5% neuromuscular transmission (T_5) after an initial bolus in determining the infusion requirements for mivacurium or suxamethonium.

PATIENTS AND METHODS

We studied 30 healthy adults (ASA physical status I or II) aged 18–57 yr. All patients underwent low to moderate risk elective surgical procedures requiring tracheal intubation. Women of childbearing age were excluded. No patient received aminoglycoside antibiotics or antihistamine drugs within 48 h of the study, which was approved by the Institutional Review Board of Presbyterian Hospital. Informed consent was obtained from each participant.

Patients received diazepam 0.1–0.2 mg kg^{-1} by

SUMMARY

Mivacurium chloride is a new, short-acting non-depolarizing neuromuscular blocking agent presently undergoing clinical evaluation. The neuromuscular effects of mivacurium and suxamethonium given by bolus and infusion were compared in adult patients during nitrous oxide–oxygen–opioid anaesthesia. Neuromuscular block was monitored by recording the compound electromyogram of the adductor pollicis muscle resulting from supramaximal train-of-four stimuli applied to the ulnar nerve. Time to onset of complete block and recovery to T_5 *were significantly shorter for suxamethonium than for mivacurium (1.0 (0.1)* v. *2.5 (0.3) min and 6.4 (0.7)* v. *17.5 (1.8) min; mean (SEM)). Conditions for tracheal intubation were similar in the two groups although intubation was performed 0.75–1.3 min later following mivacurium. The infusion rate required to maintain neuromuscular block was 88.6 (10.4) µg kg*$^{-1}$ *min*$^{-1}$ *for suxamethonium and 7.8 (1.2) µg kg*$^{-1}$ *min*$^{-1}$ *for mivacurium. There was a significant negative correlation between recovery to* T_5 *and infusion rate for mivacurium and for suxamethonium. It was equally easy to titrate the infusion rate to the desired degree of block in each group. The recovery index (*T_{25}*–*T_{75}*) after the infusion stopped was similar in patients who received mivacurium and those who received suxamethonium.*

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mouth) or morphine 0.05–0.10 mg kg^{-1} i.m. with hyoscine or atropine 1 h before anaesthesia was induced. Venous blood samples were obtained before operation for measurement of plasma cholinesterase activity and dibucaine number. Anaesthesia was induced with thiopentone 3–10 mg kg^{-1} and fentanyl 1–6 µg kg^{-1} i.v. and maintained with 70% nitrous oxide in oxygen; additional thiopentone or fentanyl was given as needed.

After induction of general anaesthesia the ulnar nerve was stimulated supramaximally with repeated trains-of-four (TOF) (2 Hz for 2 s at 20-s intervals) via surface electrodes at the wrist. The evoked compound electromyogram of the adductor pollicus muscle was recorded using a Datex monitor. The arm was positioned on an armboard and protected from movement by surgical drapes. Temperature of the hand was not measured. A single bolus of either suxamethonium 1 mg kg^{-1} or mivacurium 0.25 mg kg^{-1} was administered over 5 s through a T-connector into a rapidly flowing i.v. infusion. Patients were allocated randomly to receive either mivacurium or suxamethonium.

The percent neuromuscular block resulting from the bolus and infusion of drug was calculated from the amplitude of the first of the TOF responses (T1) at that time compared with the T1 response before drug administration. After the infusion was stopped, recovery was determined from the amplitude of the maximum, stable T1 response at the end of the study; at this time the TOF ratio (T4:T1) was greater than 0.9.

Tracheal intubation was attempted 1 min after the bolus of suxamethonium or 1.5 min after the bolus of mivacurium if at least 80% neuromuscular block had been achieved. If the block was less than 80%, the attempt was delayed until $\geqslant$ 80% block was established. Because of the study design, any cardiovascular effects of the blocking agent *per se* could not be distinguished from those related to laryngoscopy and intubation and are, therefore, not reported. Conditions for intubation were scored as: excellent (no resistance to laryngoscopy, no movement of the vocal cords, no movement of the diaphragm, and no coughing after intubation); good (no resistance to laryngoscopy, no movement of the vocal cords, but slight coughing or movement of the diaphragm after intubation); fair (no resistance to laryngoscopy, but movement of the vocal cords and coughing after intubation); poor (intubation could not be accomplished because of patient movement or coughing).

When neuromuscular transmission returned to approximately T_5 after the initial dose of blocking drug, a continuous infusion of mivacurium or suxamethonium was started. The infusion was continued for as long as surgical relaxation was needed. The infusion rate was adjusted to maintain neuromuscular block between 89 and 99%. Mivacurium 0.2 mg ml^{-1} or suxamethonium 2.0 mg ml^{-1} was delivered from a 250-ml macrodrop infusion burette (Abbott). (Solutions of mivacurium 0.5 mg ml^{-1} in 5% Dextrose are stable at room temperature for at least 48 h.) The volume of myoneural blocker infused was noted every 3 min. The infusion rate (IR) (µg kg^{-1} min^{-1}) needed to maintain block at 89–99% was then calculated. The number of 3-min epochs during which neuromuscular block was outside this range was recorded.

After the infusion was stopped, spontaneous recovery of neuromuscular transmission was observed for as long as possible. The times between cessation of infusion and recovery to 5% (T_5), 25% (T_{25}), 50% (T_{50}), 75% (T_{75}), and 95% (T_{95}) of baseline were noted where available. The 5–95% (T_5–T_{95}) and 25–75% (T_{25}–T_{75}) recovery indices were calculated. If clinically indicated, residual neuromuscular block from mivacurium was antagonized with neostigmine and atropine or glycopyrrolate.

Standard errors are shown for all mean values. Data were analysed where appropriate by linear regression, two-tailed Student's *t* test, Mann–Whitney test, or chi-square analysis. The correlation between time from injection of the bolus of either suxamethonium or mivacurium to recovery of neuromuscular transmission to T_5 and the steady-state infusion rate was tested by a linear least-squares regression analysis. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Bolus doses of mivacurium and suxamethonium

Sixteen patients were given suxamethonium and all developed complete neuromuscular block after the initial bolus dose. Twelve of the 14 patients who received mivacurium 0.25 mg kg^{-1} developed complete block after the initial bolus dose. Two of the patients given mivacurium had less than 50% block 90 s after the initial bolus and were given a supplementary bolus dose (0.02 and 0.10 mg kg^{-1}). Because the second dose of mivacurium was given before maximal block developed, these patients were excluded from analysis of onset time, intubation efficacy and correlation between T_5 and infusion rate. The mean (SEM) time from administration of the initial bolus dose to maximum neuromuscular block (onset time) was 2.5 (0.3) min for patients given mivacurium and 1.0 (0.1) min for patients given suxamethonium (table I). The mean time from administration of the initial dose of blocking drug to recovery to T_5 was 17.5 (1.8) min after mivacurium and 6.4 (0.7) min after suxamethonium.

The time from administration of the neuromuscular blocker to tracheal intubation was less for suxamethonium than for mivacurium. Four of the 12 patients given a single dose of mivacurium met the criterion for neuromuscular block and underwent successful intubation 1.5 min after the dose. In eight of 12 patients < 80% blockade was present after 1.5 min and intubation was delayed. In one of these patients intubation was attempted 1.7 min after the mivacurium dose and was unsuccessful because of factors other than the depth of anaesthesia and the degree of block. This patient was therefore excluded from analysis of intubation conditions. The mean time from administration of mivacurium to successful intubation was 2.0 (0.2) min (range 1.5–3.3 min; $n = 12$).

TABLE I. *Onset and duration of action of mivacurium and suxamethonium (mean (SEM) [range])* T_5 *is time from injection to recovery of twitch response to 5% of baseline transmission* *$P < 0.05$ *between groups*

	Time to maximum block (min)	T_5 after bolus (min)
Mivacurium	2.5 (0.3)* [1.3–4.6] $n = 12$	17.5 (1.8)* [11–32.3] $n = 11$
Suxamethonium	1.0 (0.1) [0.6–1.6] $n = 16$	6.4 (0 7) [3.3–11.6] $n = 11$

Thirteen patients given suxamethonium met the criterion for neuromuscular block and intubation was performed at 1 min or earlier; one patient underwent intubation 45 s after suxamethonium. Three patients given suxamethonium underwent intubation later than the prescribed time. In one patient, < 80% block was present 1.3 min after the suxamethonium dose, but intubation was performed 1.5 min after the bolus dose, when 96% block was present. In another patient, the mouth could not be opened until 80 s after the bolus dose, despite the presence of complete block at 60 s. This patient's trachea was intubated successfully 80 s after the suxamethonium. He exhibited no increase in heart rate or temperature and the anaesthetic continued without incident. In the third patient, other aspects of his care delayed tracheal intubation despite the presence of 80% block 1 min after the suxamethonium. The mean time from administration of suxamethonium to successful intubation was 1.1 (0.1) min (range 0.75–2 min; $n = 16$). Intubation conditions were rated as excellent or good in all patients (mivacurium: excellent = 9, good = 2; suxamethonium: excellent = 12, good = 4).

One patient had transient facial flushing after the bolus dose of suxamethonium. Ten of the 14 patients given mivacurium had facial or truncal flushing, or both, after the bolus dose. Flushing in both the suxamethonium and the mivacurium-

TABLE II. *Infusion characteristics and spontaneous recovery data for mivacurium and suxamethonium (mean (SEM) [range]).* *$P < 0.05$

			Recovery indices after infusion	
Drug	Duration of infusion (min)	Infusion rate (μg kg^{-1} min^{-1})	T_5–T_{95} (min)	T_{25}–T_{75} (min)
Mivacurium	60.4 (9.5) [15–138] $n = 14$	7.8 (1.2)* [3.6–20 4] $n = 14$	14.0 (1.0) [12.3–16.4] $n = 4$	5.6 (0.7) [4.0–11.3] $n = 10$
Suxamethonium	55.1 (7.0) [14–111] $n = 16$	88.6 (10.4)* [40–165] $n = 16$	12.3 (1 3) [8.6–16.7] $n = 6$	5.7 (0 8) [1.6–11.3] $n = 14$

treated patients disappeared in less than 5 min. No patient developed urticaria, bronchospasm or evidence of altered pulmonary compliance.

Infusion of mivacurium and suxamethonium

Fourteen patients received mivacurium and 16 patients received suxamethonium by infusion. The mean duration of infusion was aproximately 1 h in both groups (table II). The mean rate of infusion needed to maintain neuromuscular block at 89–99 % of control was 7.8 µg kg^{-1} min^{-1} for mivacurium and 88.6 µg kg^{-1} min^{-1} for suxamethonium (table II). When initial adjustments in infusion rate had been made, there was no tendency for the rate to increase or decrease systematically during the remainder of the infusion period. The average infusion rates varied widely among individual patients receiving mivacurium (3.6–20.4 µg kg^{-1} min^{-1}) or suxamethonium (40–165 µg kg^{-1} min^{-1}) (table II). There was no significant difference between the variability of the infusion rates for mivacurium or suxamethonium. The number of 3-min epochs during infusion that started and ended within desired limits (89–99 % block) were similar for the two agents (chi-square test). The number of such epochs during infusion was 155/203 for mivacurium (76 %) and 128/180 for suxamethonium (71 %).

After the infusion was stopped, the rate of spontaneous recovery of neuromuscular transmission, as assessed by the 5–95 % and 25–75 % indices, was similar for mivacurium and suxamethonium (table II). Three patients given suxamethonium showed evidence of phase II block at the time of cessation of infusion (T4:T1 ratio < 0.50). Data from these patients did not significantly change the average recovery indices for suxamethonium and are therefore included in table II. Two of these patients were given neostigmine 0.035 and 0.044 mg kg^{-1}, respectively, at 94 % and 87 % recovery of T1. The TOF ratios were 0.55 and 0.52, respectively, at that time. Times of recovery of TOF ratio to ⩾ 0.75 were 2.3 and 3.0 min and times to T1 ⩾ 95 % were 0.6 and 2.3 min after administration of neostigmine.

In six patients who received mivacurium by infusion the TOF ratio spontaneously recovered to > 0.75 by 21.4 (3.3) min (12.6–34.3 min). Residual neuromuscular block was antagonized in five patients given mivacurium with neostigmine 0.014–0.044 mg kg^{-1} at degrees of recovery ranging from 54 % to 89 %. In these patients the times from administration of neostigmine to the time when TOF ratio ⩾ 0.75 were 1.0 to 7.0 min and times to T1 ⩾ 95 % ranged from 1.3 to 3.3 min.

Plasma cholinesterase activity and dibucaine numbers for all patients who received mivacurium were within the normal range (2.4–6.2 iu litre^{-1} and 73–90 %, respectively). Two patients who received suxamethonium had normal plasma cholinesterase activity but low dibucaine numbers (66 % and 68 %). These two patients had less than average infusion rates (60 and 40 µg kg^{-1} min^{-1}). One had a shorter than average (T_{25}–T_{75} = 3.7 min) and one had a longer than average (T_{25}–T_{75} = 9.0 min) recovery index after cessation of infusion. Overall, there was no significant correlation between plasma cholinesterase activity or dibucaine number and time to recovery to T_5, recovery indices or infusion requirements in patients given mivacurium or suxamethonium. Therefore, the results from the two patients with a low dibucaine number were included in calculation of the neuromuscular effects of suxamethonium.

Relationship of recovery time and infusion rate

The relationship between recovery to T_5 and infusion rate was determined for 11 patients in the mivacurium group and 11 patients in the suxamethonium group. There was a significant nega-

TABLE III *Relationship of* T_5 *and infusion rate (mean (SEM) [range]).* T_5 *is time from injection to recovery of twitch response to 5 % of baseline transmission. Linear regression equations: mivacurium,* $IR = 13 - 0.4 \times T_5$, *suxamethonium,* $IR = 189 - 14 \times T_5$

Drug	T_5 after bolus (min)	Infusion rate (µg kg^{-1} min^{-1})	r
Mivacurium (n = 11)	17.5 (1.8) [11–32.3]	6.7 (1.0) [3.6–13.5]	0.66
Suxamethonium (n = 11)	6.4 (0.7) [3.3–11.6]	98.7 (12.6) [56–165]	0.83

tive correlation between recovery to T_5 and infusion rate for both agents (table III).

DISCUSSION

The ED_{95} for mivacurium in adults [1] is 58 $\mu g\ kg^{-1}$; mivacurium 250 $\mu g\ kg^{-1}$ was used in this study—approximately four times the ED_{95}. Suxamethonium 1 $mg\ kg^{-1}$ was estimated as an equipotent dose of four times the ED_{95} [9]. The time from injection to maximum block (onset time) was significantly shorter after suxamethonium than after mivacurium. This may reflect fundamental differences in the mechanism of action between non-depolarizing and depolarizing neuromuscular blocking agents [10]. With large doses of thiopentone supplemented by opioids or topical or i.v. lignocaine, or both, the trachea can be intubated without blockade in many patients. However, we decided not to attempt intubation unless at least 80% neuromuscular block was present. Intubating conditions at maximum neuromuscular block were comparable with both agents. Most patients given mivacurium had facial or truncal flushing, or both, which we presume was a peripheral manifestation of histamine release [11,12].

After a bolus of suxamethonium, neuromuscular transmission recovered to 5% approximately 10 min earlier than after mivacurium. There was no relation between the time to recovery to T_5 and plasma cholinesterase activity or dibucaine number in the mivacurium or suxamethonium-treated patients in this study. This is not surprising, as extremely prolonged neuromuscular block after suxamethonium is seen only with a profound decrease in plasma cholinesterase activity [13]. The duration of neuromuscular block after this bolus of mivacurium (0.25 $mg\ kg^{-1}$) appears to be approximately 50% the duration of block after intubating doses of atracurium 0.4–0.5 $mg\ kg^{-1}$ or vecuronium 0.10–0.14 $mg\ kg^{-1}$ [14–17].

In order to achieve quickly a steady-state plasma concentration of drug and, hence, a uniform degree of neuromuscular block, we began the infusion of relaxant after demonstrating the onset of recovery of neuromuscular transmission from the initial bolus dose. This study suggests that the initial infusion rate for an individual patient can be estimated from the time to 5% recovery after a bolus dose of four times the ED_{95} of either mivacurium or suxamethonium and the appropriate regression equation. In clinical practice, T_5 is the time when the first twitch of the train-of-four is again palpable. Because of the four- to six-fold variation in individual infusion requirements, the infusion should thereafter be titrated to the response of the patient. Individual variability in the average infusion requirement has been noted also for atracurium and vecuronium [18–22]. Neuromuscular block was maintained easily and controlled within a narrow therapeutic range for both suxamethonium and mivacurium administered with a simple infusion device. The infusion requirement was approximately 10-fold greater for suxamethonium than for mivacurium.

The recovery indices (T_{25}–T_{75}) after infusions of suxamethonium or mivacurium were approximately 6 min. The recovery index of mivacurium after a bolus dose is also about 6 min [1]. The recovery index of mivacurium thus appears to be independent of dose given as either a bolus or an infusion. The recovery index of suxamethonium after an infusion appears longer than that from a single dose [23] and is presumably related to the gradual development of a phase II block.

Mivacurium has a longer onset time than suxamethonium and may be associated with a greater incidence of histamine release after rapid bolus administration. The duration of action and rate of spontaneous recovery appear to be markedly shorter for mivacurium than for any currently available non-depolarizing neuromuscular blocking agent. Maintenance of continuous blockade by infusion is accomplished as easily with mivacurium as with suxamethonium and is not accompanied by the phase II block associated with suxamethonium. Individual infusion requirements can be estimated from the time to T_5 recovery after an initial bolus.

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TRANSILLUMINATED TRACHEAL INTUBATION

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SUMMARY

We evaluated the use of an inexpensive transilluminating light wand for tracheal intubation Expertise in its use was acquired quickly, thereby providing successful per-oral intubation in all patients who were able to open the mouth, irrespective of the view obtained of the epiglottis and larynx.

Occasional difficulty in tracheal intubation is a feature of clinical anaesthesia. Guided intubation using transillumination of neck tissue was described first by Yamamura, Yamamoto and Kamiyama in 1959 [1]. The first study of its use was published by Ducrow [2] in 1978 and commented upon by Rayburn [3]. Further accounts have followed [4–13]. In earlier studies, the transilluminator used was the Flexilum surgical light, but its bulb had a tendency to become detached [4,7,8] and so the instrument was modified for specific use in the trachea and it was named the Tube-Stat. This is a semi-flexible illumination wand with a battery handle. It is suited ideally for the double function of a tube strengthening stylet and a source of transillumination. The flexible shaft is 25 cm in length and therefore protrudes when placed within a cut tracheal tube.

We devised a tubular spacer to add effective length to the cut tracheal tube and, by friction, to grip the stylet handle, thereby making the assembly rigid during handling. The bulb is advanced to within 1 cm of the tip of the tube by longitudinal movement of the stylet within the tracheal tube and spacer (fig. 1).

The instructions supplied for use with the wand are complex. In practice, the manipulations suggested by the manufacturer have not proved necessary, and we believe a simplified practice such as that described below would help to encourage the use of this device.

A method for grading difficulty in intubation based on laryngoscopic view has been suggested by Cormack and Lehane [14]: grade 1 = most of the glottis is visible; grade 2 = only the posterior extremity of the glottis is visible; grade 3 = only the epiglottis is visible, no part of the glottis can be seen; grade 4 = not even the epiglottis can be seen.

The purpose of this study was to determine the relationship between the grade of laryngeal view and the subsequent ease of tracheal intubation by transillumination.

METHODS

After a period of familiarization, the manufacturer's instructions for use were abandoned in favour of the following technique.

A lubricated Portex Blue-Line tracheal tube was cut to the appropriate length, the light wand inserted into the tube and shaped to a slightly exaggerated pharyngo–laryngeal curve. With the operator standing at the head of the patient (as for laryngoscopic intubation) the thumb of the operator's gloved left hand was placed in the floor of the mouth behind the symphysis menti and the lower jaw was gently lifted anteriorly to move the tongue and epiglottis away from the posterior pharyngeal wall.

The room was darkened while the illuminated apparatus was introduced by the right hand into the right side of the mouth, directing the tip towards the left. In all cases a brilliant transillumination was observed in the skin of the left side of the neck when the tip impacted within or adjacent to the left piriform fossa (left-handed operators could perform the mirror image manipulations, but are probably more familiar with right-handed intubation, as in direct laryngoscopy).

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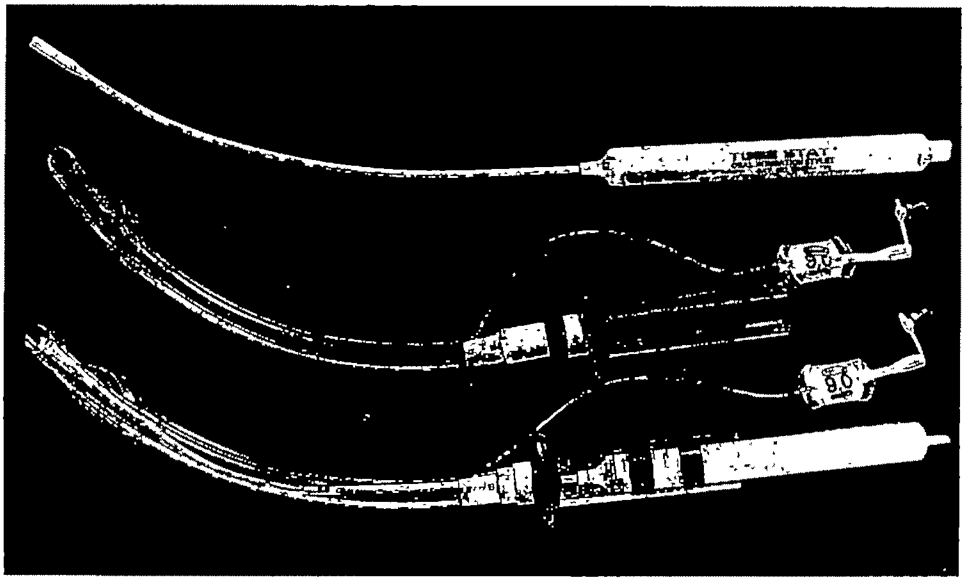

FIG. 1. The Tube-Stat illumination wand (top), tracheal tube plus spacer (middle), and assembled unit (bottom).

Observation of the intensity of the transillumination at this site indicated approximately how far into the mouth the apparatus should be inserted in order to reach the laryngeal inlet and so mitigated against any tendency of the operator to insert the tracheal tube into the oesophagus. It indicated also the light intensity that was expected subsequently when the Tube-Stat was transilluminating through the larynx and trachea. For instance, thick-necked, pigmented individuals yielded weaker transillumination than the thin, fair-skinned patient.

Subsequently, the tip of the apparatus was withdrawn slightly and then advanced in the midline, first towards the posterior pharyngeal wall and then anteriorly to reach the glottis. The final approach and entry into the larynx produced intense transillumination, always greater than that previously identified in the neck. The shadows of the laryngeal cartilages were often apparent at this stage. Further advancement demonstrated a bright ball of light descending down the midline and slightly towards the left. If oesophageal passage occurred, while a transillumination was often apparent, it was more diffuse and its intensity was markedly less than that observed first in the neck.

After initial familiarization and practice with the Tube-Stat, we studied 200 patients requiring tracheal intubation for their anaesthetic management. They were prepared for intubation under general anaesthesia with an intubating dose of a neuromuscular blocker and ventilation of the lungs with oxygen. Each patient was given a laryngeal view grade and received 4% lignocaine 3–4 ml by spray during laryngoscopy. Following this preparation, all intubations were executed by one of us (THH) and allocated a success score: I = success at first attempt; II = success after three attempts; III = success after multiple attempts within 1 min; IV = failure to intubate after 1 min.

The laryngeal view grade and success scores were allocated by the intubator. Successful intubation was confirmed by chest movements and auscultation.

RESULTS

Laryngoscopic view grades and success scores are shown in table I.

The frequency of grade 2 and 3 laryngeal views in our study was greater than that observed by Cormack and Lehane, possibly because of a rather large percentage of elderly mid-European patients with elaborate dental conservation in our local population.

Every trachea was intubated successfully within

TABLE I. *Number of patients allocated to each success score and each laryngoscopic view grade*

View grade	Success score I	II	III	IV	Total	%
1	154	22	2	0	178	89
2	12	0	0	0	12	6
3	8	1	0	0	9	4.5
4	1	0	0	0	1	0.5
Total	175	23	2	0	200	
%	87.5	11.5	1	0		100

1 min from the introduction of the intubating apparatus and most intubations were accomplished with ease at the first attempt. Only in one subject was difficulty experienced in relation to a "difficult" grading. In the remainder, there was no apparent correlation between "difficult" grading and intubation success scores.

DISCUSSION

Other studies have indicated that the speed and success of tracheal intubation by transillumination varies with the experience of the intubator [7, 9], but that the technique is learned easily with a minimum of practice [3, 10]. In the present study, all intubations were performed by one operator, and therefore the results may be biased towards the expert.

We believe that the grade 3 laryngeal view, which is not uncommon, causes the average anaesthetist great difficulty at intubation. In this situation, many anaesthetists would use a styletted Oxford tube, but transillumination is an alternative which has been shown to have high success rates. Grade 4 laryngeal views are rare in the general surgical population and patients in this category present great difficulty for intubation. In these subjects the styletted Oxford tube method is rarely effective and transillumination may be valuable.

It has been suggested that transillumination may be a suitable method for tracheal intubation under "field" conditions [7, 8]. Our experience suggests that satisfactory conditions are met only when a darkened environment can be obtained and that transillumination in daylight may not be a reliable indicator of successful intubation (although absolute darkness is not mandatory). While others [7, 8] have experience in Lightwand-guided intubation in emergency cases, we cannot make recommendations on its use in situations where the risk or regurgitation is high. The prevailing lighting conditions and the absence of direct laryngoscopic view preclude early recognition of regurgitation, and cricoid pressure may affect the ease of intubation.

Other studies have shown that there is no increased incidence of major or minor complications with this technique compared with laryngoscopic intubation [7, 9]. We re-used the same Tube-Stat for familiarization, throughout the study and subsequently for a total of 250 intubations. After each use, the stylet portion was sterilized with chlorhexidine in spirit 0.5% w/v. There was a reduction in light intensity of our first device which was noticeable only when compared with a new unit.

Note: The Tube-Stat is manufactured by Concept Incorporated (U.S.A.) and distributed by Henleys Medical Supplies Ltd (London). The unit costs £25.20 and it is designated as a "limited re-use instrument".

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PHARMACOKINETICS OF MORPHINE FOLLOWING ADMINISTRATION BY THE BUCCAL ROUTE

A. R. MANARA, M. P. SHELLY, K. G. QUINN AND G. R. PARK

SUMMARY

The pharmacokinetics of morphine administered via the buccal route as a controlled release formulation were assessed after the administration of three different doses and found to be linear in the dose range 10–30 mg The plasma concentrations of morphine-3-glucuronide and morphine-6-glucuronide demonstrated considerable inter-subject variation and conclusions could not be drawn regarding their pharmacokinetics These large differences may reflect not only variability in buccal absorption, but may have resulted from the preparation dissolving in saliva, followed by absorption from the gastrointestinal tract.

Morphine sulphate is an effective analgesic when administered by the parenteral or oral route [1]. However, the amount of morphine reaching the systemic circulation after oral administration is reduced by first pass metabolism in the gut wall and liver [2]. In addition, the absorption of orally administered morphine requires a functional gastrointestinal tract. This limits the use of oral morphine after operation. Both these problems may be overcome by the administration of morphine via the buccal route.

Administration of morphine by the buccal route has been shown to be effective for relief of pain after elective orthopaedic surgery [3]. However, the pharmacokinetic data from this study have been questioned [4]. Fisher, Fung and Hanna [4] concluded that buccal administration of morphine resulted in marked inter-individual variability in the concentration time profiles and, generally, lower plasma concentrations of morphine than those observed previously; this may have resulted from considerable variation in tablet persistence time on the buccal mucosa.

The present study was designed to resolve the conflicting reports from previous studies. The pharmacokinetics of morphine were investigated following three separate buccal doses of 1 × 10 mg, 2 × 10 mg, 3 × 10 mg and 1 × 30 mg of morphine sulphate tablets. An experimental controlled release formulation based on hydrophilic polymers was used (Napp Laboratories Ltd, Science Park, Cambridge, U.K.).

PATIENTS AND METHODS

An open dose ranging study of controlled release buccal morphine sulphate tablets was undertaken in 47 patients (aged 16–65 yr, weight less than 85 kg, ASA I or II [5]) undergoing gynaecological, orthopaedic or general surgery procedures. Patients with chronic disease, a history of alcohol or drug abuse, treatment with any other medication, or pregnant and lactating females were excluded. The study was approved by the Hospital Ethics Committee and written informed consent was obtained from each patient.

All patients received a standard anaesthetic technique consisting of thiopentone, nitrous oxide and isoflurane in oxygen delivered via a circle system with carbon dioxide absorption. Alcuronium was used to provide neuromuscular block and ventilation was controlled according to the Radford Nomogram [6]. Escape analgesia in the perioperative period was provided by pethidine 1 mg kg^{-1} i.m. as required.

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Fourteen patients received a single 10-mg tablet (group A); 10 received two 10-mg tablets (group B); 13 received three 10-mg tablets (group C); 10 received one 30-mg tablet (group D). Subjects in group A were allocated to two subsets, nine patients receiving a "wetted" tablet and five a dry tablet, to assess the effect of moistening the tablet on its subsequent absorption. The tablet(s) was placed in the buccal sulcus above, below, or above and below, a canine tooth 4 h before the planned start of anaesthesia and retained for 12 h. Before administration of the tablets, and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10 and 12 h after administration, blood samples were taken from an indwelling i.v. cannula into lithium heparin tubes. The blood was centrifuged for 15 min and the supernatant plasma separated and stored at −20 °C until analysis. Plasma concentrations of morphine were determined using a radioimmunoassay (RIA) technique with prior solid phase extraction to exclude metabolites [7]. The limit of detection of the RIA was 0.5 ng ml^{-1} with a coefficient of variation of 21% at the limit of detection. Plasma concentrations of morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) were assayed using high pressure liquid chromatography (HPLC) [8]. The limits of detection were 10 ng ml^{-1} and 5 ng ml^{-1} and the coefficients of variation 7.5% and 6.8% for the M3G and M6G assays, respectively. At the end of the study period any remaining tablet was recovered from the buccal sulcus and subsequent analysis of its morphine content attempted.

Areas under the plasma concentration *v.* time curves were calculated over 12 h (AUC_{12}) using the trapezoidal method [9]. Maximum observed plasma concentrations (*C*max) and the times to these values (*T*max) were obtained directly from the observed data. In order to assess the linearity in the pharmacokinetics of morphine and the two metabolites, the AUC_{12} and *C*max values were adjusted to account for dose (AUC_{12}/D and $C\max/D$). The AUC_{12}/D and $C\max/D$ values from different doses were compared using unpaired *t* tests and *T*max values were compared using the Kruskal–Wallis test.

RESULTS

There were no significant differences between groups with regards to age (mean (SD)), 39(11), 39(13), 39(13) and 39(12) yr for groups A–D, respectively), weight (61(9), 61(8), 62(7) and

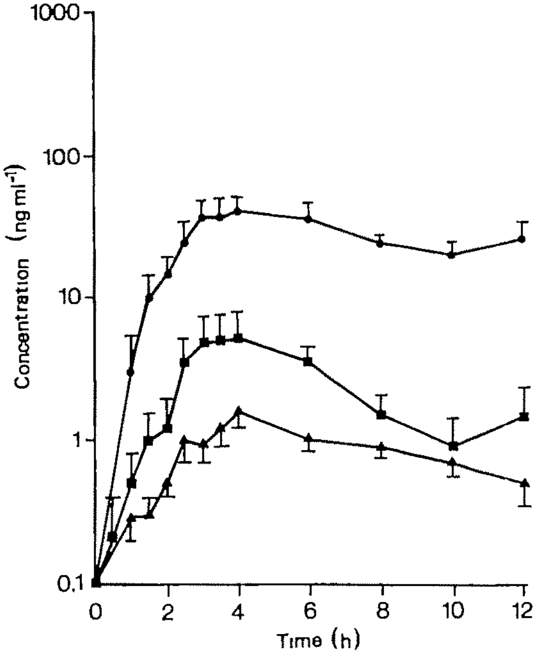

FIG. 1. Mean (SEM) plasma concentrations of morphine (▲), M3G (●) and M6G (■) following the administration of morphine sulphate 10 mg (group A).

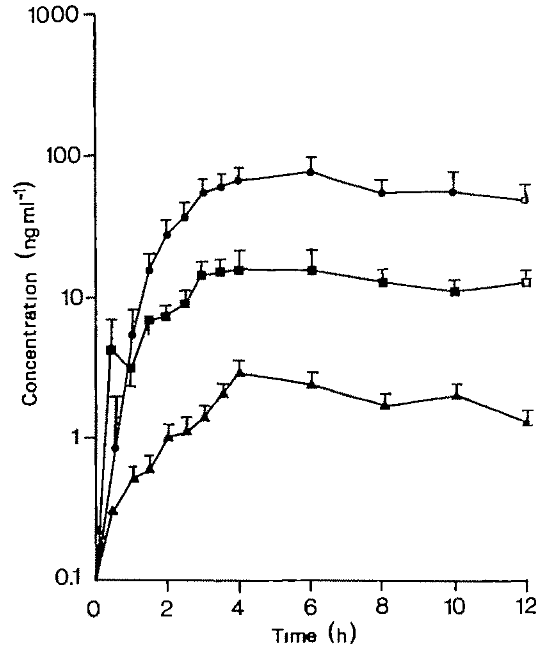

FIG. 2 Mean (SEM) plasma concentrations of morphine (▲), M3G (●) and M6G (■) following the administration of 2 × morphine sulphate 10 mg (group B).

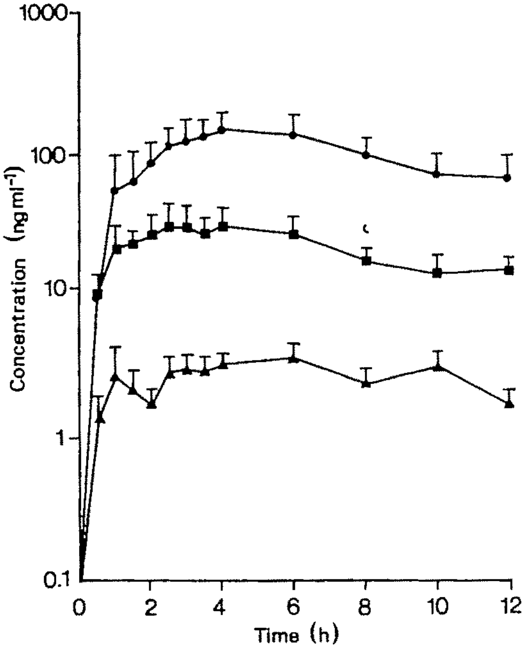

FIG. 3. Mean plasma concentrations of morphine (▲), M3G (●) and M6G (■) following the administration of 3 × morphine sulphate 10 mg (group C).

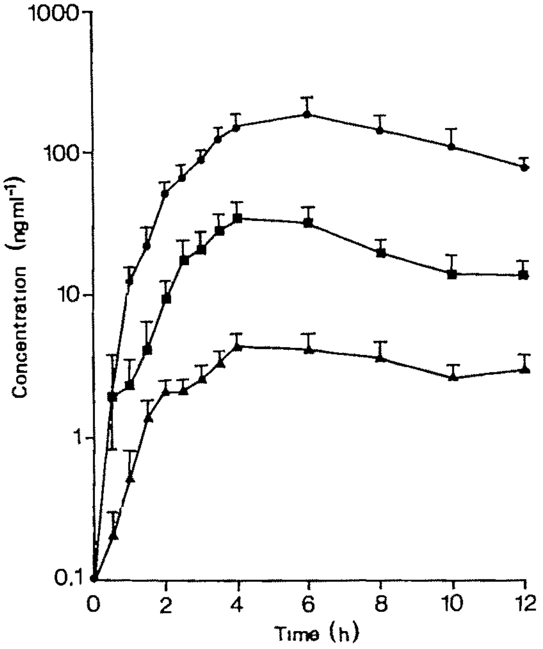

FIG. 4. Mean plasma concentrations of morphine (▲), M3G (●) and M6G (■) following the administration of 1 × morphine sulphate 30 mg (group D).

63(9) kg, groups A–D, respectively) and sex. Of the patients who started the study, 43 completed pharmacokinetic evaluation. There were no significant differences between any of the pharmacokinetic parameters derived from patients receiving the 10-mg tablet in the wetted or dry states. Therefore these subjects were combined to form group A and compared with the other groups. The mean plasma *v.* time profiles for morphine, M3G and M6G at the different doses are illustrated in figures 1–4. The derived pharmacokinetic parameters are listed in table I.

The mean *C*max/*D* values for morphine were 0.20, 0.20, 0.16 and 0.20 ng ml^{-1} mg^{-1} for groups A–D, respectively. The corresponding values for AUC$_{12}$/*D* were 0.89, 1.03, 0.93 and 1.19 ng h ml^{-1} mg^{-1}. There were no significant differences between the four dose groups for the values of

TABLE I. *Pharmacokinetic parameters (mean (SD); median and range for* T*max) of morphine, M3G and M6G following administration of morphine sulphate by the buccal route*

	Group	AUC$_{12}$ (ng h ml^{-1})	AUC$_{12}$/*D* (ng h ml^{-1} mg^{-1})	*C*max (ng ml^{-1})	*C*max/*D* (ng ml^{-1} mg^{-1})	*T*max (h)
Morphine	A	8.9 (5.8)	0.89 (0.58)	2.0 (1.1)	0.20 (0.11)	4.0 ((2.5–12.0)
	B	20.5 (8.5)	1.03 (0.43)	4.0 (2.1)	0.20 (0.11)	4.2 (3.5–10.0)
	C	28.0 (13.3)	0.93 (0.44)	4.8 (2.1)	0.16 (0.07)	6.0 (1.5–6.0)
	D	35.6 (11.2)	1.19 (0.37)	6 0 (1.9)	0.20 (0.06)	5.5 (1.5–12.0)
M3G	A	260.4 (114.3)	26.1 (11.4)	56.8 (28.8)	5 7 (2 9)	4.0 (3.0–12.0)
	B	611.1 (332.6)	30 6 (16 6)	103.4 (56.1)	5.2 (2.8)	5.0 (3.0–12 0)
	C	1215.6 (1045.5)	40.5 (34.9)	202.7 (199.2)	6.8 (6.6)	4.0 (3.5–12.0)
	D	1323.1 (985.2)	44.1 (32.8)	225 6 (176.1)	7.5 (5.9)	6.0 (3.5–24.0)
M6G	A	23.2 (19.6)	2.3 (2.0)	6.9 (4.8)	0.69 (0 48)	3.8 (3.0–12 0)
	B	142.1 (76.4)	7.1 (3.8)	28.0 (14.4)	1.4 (0.72)	3.8 (0 5–24.0)
	C	227.2 (215.2)	7 6 (7.2)	51.0 (36.5)	1.7 (1.2)	4.0 (1.0–12.0)
	D	223.7 (139.7)	7.5 (4.7)	49.4 (29.4)	1 6 (1 0)	5.0 (3.5–12.0)

AUC_{12}/D and $Cmax/D$. That is, within the dose range 10–30 mg, the pharmacokinetics of morphine administered buccally were linear.

There was considerably more intersubject variability in the derived pharmacokinetic parameters for the morphine metabolites, M3G and M6G (table I). For example, the standard deviations constituted 44–95% of the estimated mean AUC_{12}/D values. The metabolite M3G achieved plasma concentrations approximately 25 times, and M6G concentrations between 3 and 10 times, those of the parent morphine. Both metabolites appeared in the plasma simultaneously with morphine and their plasma concentration profiles were approximately parallel; *T*max values were similar for all three compounds. There were no significant differences between the four groups for values of AUC_{12}/D and $Cmax/D$ for M3G and M6G.

The data on the residual morphine in the buccal tablets remnants were inconclusive and incomplete, because of inability to repeat and validate the assay with such small residues, and are therefore excluded from further analysis.

Eleven patients (78.6%) in group A, eight patients (80%) in group B; four patients (30.8%) in group C seven patients (70%) in group D required pethidine after operation.

During the course of the study it became apparent that patients complained spontaneously of a bitter taste associated with the tablet(s). Unfortunately, the exact numbers were not recorded. However, in a subsequent double-blind study 100% of patients receiving the same formulation of buccal morphine complained of a bitter taste, compared with 20% in the placebo group (unpublished observations).

DISCUSSION

The consistent values obtained for the dose-adjusted AUC_{12} and *C*max values indicated that the pharmacokinetics of morphine are linear across the plasma concentration–buccal dose range. Furthermore, equivalence was demonstrated between the 3 × 10 mg and 1 × 30 mg tablets. The latter observation suggests that neither the surface area of the tablets nor the buccal mucosa exposed to parent morphine were important determinants of the rate or extent of buccal absorption. There was wide inter-subject variability in the pharmacokinetic parameters derived for M3G and M6G. The concentrations of both compounds increased with dose in a linear fashion. The concentrations of both metabolites reflect those of morphine in the plasma.

Many of the patients in all groups complained of a bitter taste; for this to occur morphine sulphate must have dissolved in saliva. In addition, the bitter taste would have promoted the swallowing reflex, resulting in transfer of morphine into the systemic circulation, not only from the buccal sulcus but also via the gastrointestinal tract. The objective of avoiding first pass metabolism, therefore, was probably not achieved. Adminstration of such tablets to patients with postoperative ileus could result in the accumulation of large amounts of morphine in salivary solution in the stomach and with the return of bowel function the morphine may be dumped into the small bowel, absorbed and potentially precipitate opioid toxicity.

Our results may also provide some explanation for the discrepancies found in different studies [3, 4]. Bell and colleagues [3] described the tablet as "sticking to the buccal mucosa". In this case the morphine could pass directly into the mucosa and into the systemic circulation. It is conceivable that Fisher, Fung and Hanna [4] encountered a problem similar to that encountered in the present study, notably, dissolution of morphine and absorption via the gastrointestinal tract. In support of this argument, the *C*max and AUC values quoted by them [4] were similar to those determined in this study and their patients also complained of a bitter taste.

Although fewer patients in the higher dose groups required pethidine after operation, no conclusions can be drawn on the ability of this formulation to provide adequate analgesia; the operative procedure was not standardized, the study was open and there was no control group. A double-blind study is being undertaken to assess the analgesic efficacy of the formulation. It is possible that masking flavours may be necessary if this route of administration of morphine is to prove acceptable to patients [10], especially if the tablet is to be retained over a prolonged period of time.

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SAFETY AND EFFICACY OF A LOW VOLUME EXTRADURAL TEST DOSE OF BUPIVACAINE IN LABOUR

G. D. PRINCE, G. R. SHETTY AND M. MILES

The majority of extradural blocks performed in the U.K. are for analgesia in labour. Accidental intravascular and subarachnoid injections of local anaesthetic may occur if the catheter is misplaced. Intravascular injection of the therapeutic dose is unlikely to be dangerous provided it is fractionated, injected slowly and comprises less than 35 mg of bupivacaine [1].

Accidental intrathecal injection of the therapeutic dose may cause total spinal block. A test dose of local anaesthetic is widely recommended as a method of preventing this complication, but guidelines vary widely [2–4]. Large studies of obstetric and non-obstetric extradural blocks confirm that a test dose is often effective in preventing total spinal block. However, these same reports describe occasional instances where, despite use of the test dose, further injection of local anaesthetic has been administered intrathecally [5–7]. These cases suggest that misinterpretation of the extradural test dose is possible.

Ideally a test dose should produce clear evidence of subarachnoid injection rapidly and safely. Interpretation should be easy and false positive and false negative results should not occur.

Bupivacaine 0.5 % has been used as an obstetric extradural test dose in a variety of volumes [8–10]. Kumar, Dennison and Panchal [8] have recommended a low volume (1.5 ml) bupivacaine test dose following their experience of spinal anaesthesia with 1.6 ml of 0.5 % bupivacaine for Caesarean section [11]. This study was designed to assess the safety and effectiveness of a 1.6-ml test dose in healthy pregnant females.

SUMMARY

A low volume of bupivacaine has been recommended as a "test dose" before extradural injection of local anaesthetic in labour. In order to test the safety and efficacy of this test procedure, the effects of bupivacaine 1.6 ml given by extradural injection were compared with those following the same dose given by the intrathecal route. Various indices of motor, sensory and autonomic block were recorded after injection in two groups of 20 healthy pregnant patients. Complete inability to raise the foot from the bed by hip flexion with the knee held straight was the only definite sign of intrathecal injection. In 10% of patients the final diagnosis could not be made until 10 min after injection. In 25% of patients hypotension occurred within 5 min of intrathecal injection despite preload with 1 litre of fluid i.v.

PATIENTS AND METHODS

All patients involved in the trial gave informed written consent for the investigation which was approved by the district Ethics Committee. Baseline data obtained in all subjects included age, weight on admission, height and parity, and arterial pressure and heart rate in the left lateral horizontal position. The behaviour of a 1.6-ml test dose of isobaric 0.5 % bupivacaine was compared in the subarachnoid space (group I) and in the extradural space (group II) in pregnancy.

Group I comprised 20 healthy pregnant females requesting regional anaesthesia for elective Caesarean section. After premedication with ranitidine 150 mg by mouth 2 h before operation and

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0.3-mol litre^{-1} sodium citrate 30 ml given when the patient arrived in the theatre, an i.v. infusion was commenced and a preload of 1 litre of Hartmann's solution or normal saline was given. The patient was placed in the left lateral horizontal position and a needle inserted into the extradural space at the L2/3 or L3/4 space. A long 26-gauge spinal needle was passed through the extradural needle until the dura was penetrated. After a small volume for apparatus deadspace was allowed, isobaric 0.5% bupivacaine 1.6 ml was injected into the subarachnoid space and the spinal needle was removed. A catheter was then passed through the Tuohy needle into the extradural space and secured in the usual manner. The patient was turned to the supine position with 15° of lateral tilt and the onset of block was observed at 3, 5, 7.5 and 10 min after the injection of the local anaesthetic.

Pinprick sensation was studied at four sites on each leg: the groin (L1); the medial side of the knee (L3); the top of the foot (L5) and the back of the thigh (S2). Sensory block was scored as 0 = normal sensation; 1 = touch sensation only (analgesia); 2 = no sensation (anaesthesia). The maximum height of block was assessed 30 min after injection as the highest recorded level of abnormal pinprick sensation (grade 1 or 2 sensory block).

The patient was asked to lift each foot in turn from the bed by flexing the hip with the knee fully extended, to assess motor block. Ability was scored as 0 = normal strength; 1 = some weakness as perceived by patient or examiner; 2 = inability to raise the straight leg.

Arterial pressure and heart rate were recorded using an automated, non-invasive arterial pressure monitor. Hypotension was defined as a systolic pressure of 90 mm Hg or less and was treated in the first instance with ephedrine 5 mg i.v. This was repeated at the second occurrence. Persistent hypotension was treated by infusing Hartmann's solution 0.5–1 litre rapidly and further 5-mg increments of ephedrine as required.

Group II comprised 20 healthy pregnant females who had not had previous opioid analgesia and who requested extradural anaesthesia for pain relief in labour. Each patient was preloaded with 1 litre of Hartmann's solution or normal saline and an extradural catheter was inserted and secured at the L2/3 or L3/4 space. After a small volume for apparatus deadspace was allowed, 0.5% bupivacaine 1.6 ml was injected into the extradural space. The patient was turned to the supine position, but with a wedge under her back designed to produce 15° left lateral tilt. Onset of block was observed in the same way as in group I, with the single exception that final block height at 30 min after injection was not recorded as the therapeutic dose of local anaesthetic had already been injected by this time.

Baseline anthropometric data and cardiovascular changes were compared using Student's t test, Mann–Whitney U test and Chi-square test.

RESULTS

There were no significant differences between the two groups in mean age, weight and height, or systolic and diastolic arterial pressure, but parity and baseline heart rate were significantly higher in group I (table I).

Onset of sensory block

Sensory analgesia and anaesthesia occurred in both groups during the 10 min after injection, but were common and more extensive in group I. In both groups, analgesia was more widespread and occurred earlier than anaesthesia. Whilst analgesia was noted in all patients in group I within the 10-min test period, by 5 min at least one dermatome was analgesic in 40% of patients in group II (fig. 1). Analgesia in all four dermatomes tested was common 5 min after spinal injection and universal by 10 min (fig. 2). Two patients had analgesia to pinprick in all four dermatomes after extradural injection, at both 5 and 10 min. This was not associated with anaesthesia, failure to raise a straight leg or hypotension at any stage. Anaesthesia was far less common in group II patients, occurring in no patient within 5 min of

TABLE I. *Mean (SD) values for baseline physiological data.* *$P < 0.05$; **$P < 0.001$. † *Median (range)*

	Group I (Subarachnoid)	Group II (Extradural)
Age (yr)	27.5 (5.0)	25.0 (5.7)
Weight (kg)	62.1 (9.2)	62.1 (10.1)
Height (m)	1.60 (0.07)	1.62 (0.05)
Parity	1 (0–4)†	0 (0–3)†**
Systolic AP (mm Hg)	127 (17)	124 (12)
Diastolic AP (mm Hg)	75 (11)	78 (13)
Heart rate (beat min^{-1})	94 (19)	81 (11)*

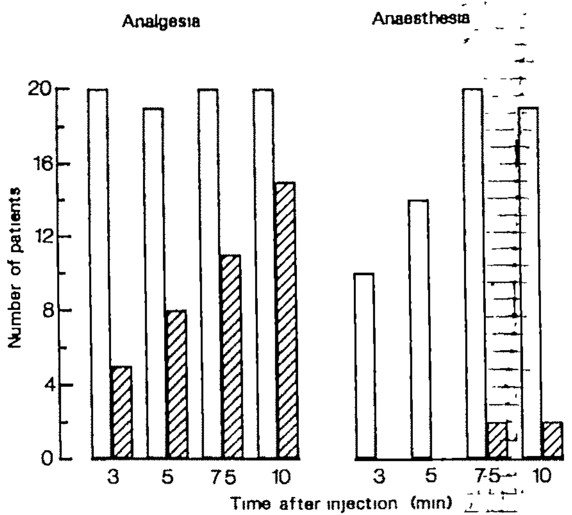

FIG. 1. Frequency of changes of pinprick sensation during the first 10 min after subarachnoid (group I: □) or extradural (group II: ▨) injection of the test dose.

extradural injection and in only 10% within 10 min. Sensory anaesthesia was not universal after spinal injection, with no anaesthetic dermatomes in 30% of group I patients at 5 min and 5% at 10 min after injection.

Maximum cephalad spread of block

Maximum cephalad spread of block was studied in group I (fig. 3). The mean maximum block height was T4 on the left and T5 on the right, but there was considerable variability between patients. The highest block attained was C4 on the left and C7 on the right and several patients had high thoracic blocks. No patients suffered difficulty with breathing, coughing or head lifting.

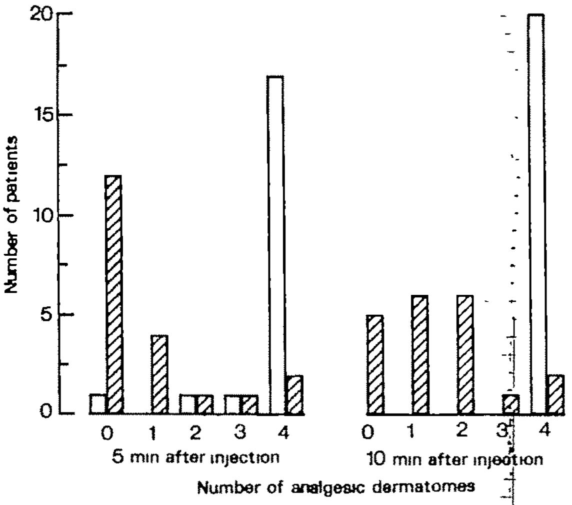

FIG. 2. Proportion of dermatomes tested which were analgesic to pinprick at 5 and 10 min after injection of the test dose. □ = Group I (subarachnoid); ▨ = group II (extradural).

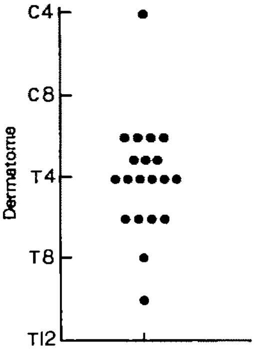

FIG. 3. Maximum cephalad spread of sensory block after subarachnoid injection of the test dose.

Onset of motor block

Patients in both groups complained of weakness of the legs when attempting to raise a straight leg, although this was commoner in group I. Total inability was present in at least one leg in 85% of patients in group I at 5 min and in all patients by 10 min after injection. All patients in group II could raise a straight leg at all times (fig. 4).

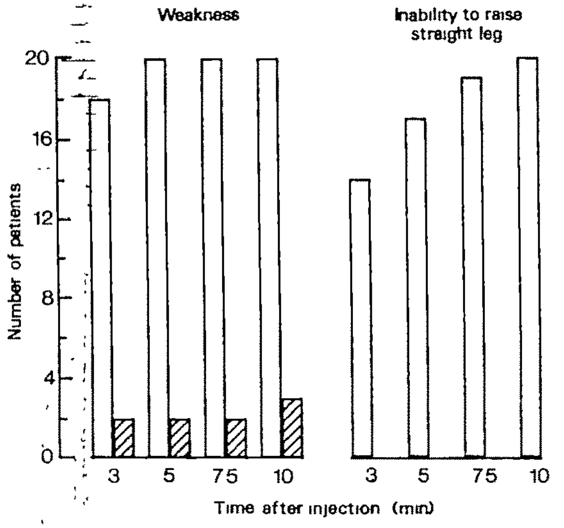

FIG 4. Frequency of changes in the ability to raise a straight leg during the first 10 min after subarachnoid (group I: □) or extradural (group II: ▨) injection of the test dose.

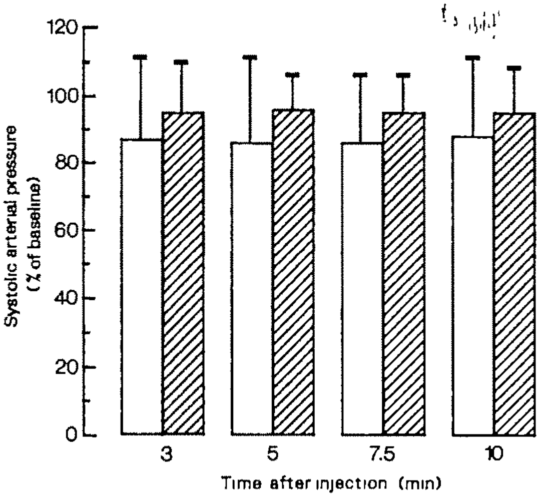

FIG. 5. Decrease in systolic arterial pressure from baseline (mean (SD)) during the first 10 min after subarachnoid (group I: □) or extradural (group II: ▨) injection of the test dose. Decreases were significant ($P < 0.01$ for group I, $P < 0.05$ for group II).

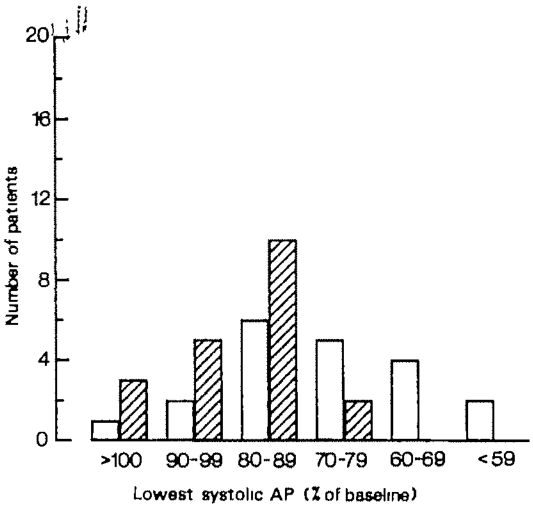

FIG. 6. Lowest systolic arterial pressure recorded within 10 min of injection of the test dose expressed as a percentage of baseline. □ = Group I (subarachnoid); ▨ = group II (extradural).

Cardiovascular changes

Significant reductions in systolic arterial pressure occurred in both groups after injection of local anaesthetic (Student's t test for paired data) (fig. 5), but those in group I were significantly larger than those in group II ($P < 0.01$, Student's t test) (fig. 6).

Hypotension (systolic arterial pressure < 90 mm Hg) occurred significantly more often in group I ($P < 0.05$, Chi-square test), affecting three patients within 3 min, five by 5 min and nine patients within the 10-min test period. In comparison, only two patients in group II were affected, both at the 3-min observation. Significantly more ephedrine was used in group I (4.5 (6) mg) than group II (0.5 (1.5) mg) ($P < 0.05$, Mann–Whitney U test) and additional fluid was necessary only in group I patients.

Heart rates varied widely in both groups. The baseline heart rate was lower in group II than group I, but there was no significant change in the heart rate in either group as a result of local anaesthetic injection.

Quality of analgesia

Following the period of observation all patients in group I underwent awake Caesarean section. In five the block was considered to be inadequate and supplementary doses of 0.5% bupivacaine were injected through the extradural catheter until analgesia was adequate.

In group II, extradural block was established and maintained effectively throughout labour using incremental injections of 0.25% bupivacaine.

DISCUSSION

In this study we have examined the effectiveness of various tests of motor and sensory loss in differentiating between subarachnoid and extradural injection of a 1.6-ml plain bupivacaine test dose in pregnant women.

Analgesia to pinprick and the presence of leg weakness were extremely sensitive signs of spinal block, but both also occurred in a significant minority of women within 5 min of extradural injection of the test dose. At first sight this may seem surprising, but it is probably a result of the subjective nature of the tests. This group almost certainly contains patients who have imagined, rather than genuine, sensory or motor deficit. False positive results may be common if these indices are used to confirm subarachnoid injection and the incidence may increase if interpretation is delayed further.

The presence of complete anaesthesia to pinprick or failure to raise a straight leg occurring within 5 min of injection was diagnostic of subarachnoid injection of the test dose, but use of this time limit resulted in an incidence of false negative results of 30% (numbness) and 15% (raising straight leg), respectively. By 10 min, two patients in group II (10%) had developed pin-prick anaesthesia at L2 and one patient in group I (5%) had no evidence of pinprick anaesthesia in any dermatome. Thus confusion can be expected even after a prolonged wait if the presence of sensory block is sought as evidence of spinal block.

Complete discrimination was possible using this test dose only if motor block was tested as late as 10 min after injection. At this time raising a straight leg was impossible in at least one leg in all patients in group I, but was possible in all patients in group II.

Although a 1.6-ml bupivacaine test dose may be used effectively in labour, it is clear that great care must be taken to avoid diagnostic error. Slow onset of spinal block in some patients after 0.5% bupivacaine [12] has been implicated as a reason for failure of the extradural test dose in non-obstetric patients [13]. Several patients in group I in this study exhibited delayed or patchy onset of block. By 5 min after injection, three patients were able to raise a straight leg; in two of them the associated sensory block was very limited. In one of these no dermatome was anaesthetic, although analgesia was widespread; in the second sensory block was limited to L5 and S2. In both of these patients, test dose failure could have occurred at 5 min, yet, by 30 min after injection, the maximum block height was T10 and T6, respectively. Avoidance of errors because of delayed onset of block is necessary when using bupivacaine test doses.

Reports of high and even total spinal blocks following intrathecal injection of isobaric bupivacaine 3–4 ml in late pregnancy [10,14,15] in the presence of aorto–caval compression [16] have led to concern over the safety of this agent as a test dose. The use of 0.5% bupivacaine 1.6 ml in a large series of Caesarean sections under spinal anaesthesia has been reported [8,11], and extensive block occurred in a small number of patients. Our results are consistent with that, since one patient developed sensory analgesia in the cervical dermatomes. However, no patient experienced difficulty with coughing or breathing or exhibited a significant decrease in grip strength.

Significant hypotension occurred in both groups. After extradural injection, hypotension resulted probably from the change of position from left lateral to supine. Despite the use of lateral tilt, some degree of aortocaval compression may have occurred. In group I, hypotension was greater (fig. 6) and more prolonged. Despite the use of preload with 1 litre of fluid, 25% of patients required ephedrine within 5 min of injection of the test dose. Systemic arterial pressures as low as 60 mm Hg systolic were recorded. Accidental subarachnoid injection of this test dose in a labouring mother after minimal fluid preload is likely, therefore, to produce severe hypotension and decrease in placental blood flow.

Various other local anaesthetic preparations have been proposed for use as test doses. Several authors have recommended lignocaine in preference to bupivacaine [2,17–19], but the only study which has investigated closely its use in obstetric practice in controlled circumstances used 1.5% hyperbaric lignocaine with adrenaline [20], a formulation which is not available in the U.K. Two millilitre of this preparation produced sensory block at S2 within 3 min of intrathecal injection in all patients and this did not occur after extradural injection; however, cardiovascular changes were not reported. In comparison, the 1.6-ml bupivacaine test dose investigated here was slower to exclude intrathecal catheter placement, but equally effective. On theoretical grounds, Casey [18] recommended 5% lignocaine 2 ml in 7.5% dextrose, but shortly afterwards Bembridge, MacDonald and Lyons [21] demonstrated that intrathecal injection of hyperbaric lignocaine 1.5 ml produced blocks involving the C2 dermatome in four of 30 pregnant women. Wilton [22] proposed a test dose of 0.5% bupivacaine 3 ml for obstetric use and McKeown, Littlewood and Wildsmith [17] have suggested 2% lignocaine 4 ml. These recommendations were made following experience with spinal anaesthesia in elderly male surgical patients. Clinical evaluation of these agents may fail to confirm their safety as test doses in pregnant females.

This study has shown that it is possible to differentiate between subarachnoid and extradural injection of 0.5% bupivacaine 1.6 ml in the obstetric patient. However, slow and patchy onset of spinal block may occur in some patients following subarachnoid injection. Thus it is necessary to wait for at least 10 min after extradural injection of this volume of 0.5% bupivacaine before inadvertent subarachnoid injection may be excluded.

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EFFECT OF TIME AND ADRENALINE ON THE FETO-MATERNAL DISTRIBUTION OF BUPIVACAINE

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SUMMARY

Following lumbar extradural analgesia with 0.5% bupivacaine, the placental transfer of bupivacaine was examined in 40 women undergoing elective and 40 women undergoing emergency Caesarean section. Within each group, the patients received randomly either plain bupivacaine or bupivacaine with adrenaline 1 in 200000. Plasma bupivacaine concentrations were measured in blood samples taken simultaneously at delivery from the umbilical vein (UV), umbilical artery (UA) and maternal vein (MV). Bupivacaine concentrations in MV, UV and UA were not significantly affected by the presence of adrenaline, but were positively correlated with first dose to delivery interval (FDD) while MV and UV were inversely correlated with last dose to delivery interval (LDD). Mean ratio of UV:MV concentrations of bupivacaine was 0.346 and for UA:MV it was 0.305. There was no significant correlation between any fetal:maternal ratio and FDD or LDD. UA:UV ratio appeared to increase towards unity 30–40 min after the last dose. The presence of adrenaline was associated with an increase in UA:UV in the elective group ($P < 0.01$). In eight patients who received adrenaline there was reverse placental transfer (UA:UV > 1). There was no evidence of progressive fetal accumulation of bupivacaine beyond 30–40 min.

The use of adrenaline in extradural solutions has produced inconsistent effects on transplacental distribution of bupivacaine [1–4]. The net transfer of bupivacaine is known to depend on concentration gradient, pH gradient, binding protein gradient and umbilical flow [5]. Adrenaline may indirectly influence placental transfer of bupivacaine by its effect on placental and uterine blood flow [6–8].

It has been claimed that the low fetal:maternal (F:M) plasma concentration ratios of bupivacaine measured consistently at delivery following extradural analgesia are the result of extensive tissue uptake rather than slow placental transfer [9]. If this were so, the umbilical artery:maternal vein ratios should increase with time and bupivacaine would become progressively more toxic in the fetus during continuous extradural administration.

We have therefore studied maternal venous, umbilical venous and umbilical arterial bupivacaine concentrations at delivery in women undergoing Caesarean section under extradural blockade: both elective and emergency, after extradural analgesia in labour. We have also re-examined the effect of adrenaline on placental transfer of bupivacaine.

PATIENTS AND METHODS

Following Ethics Committee approval and informed consent, we studied 40 women undergoing elective and 40 women undergoing emergency Caesarean section under extradural blockade. This study was part of a wider project in which extradural technique, maternal effects and maternal plasma bupivacaine concentrations have been reported previously [10, 11].

All patients received 0.5% bupivacaine in an initial single fractionated 20-ml extradural dose, plus further doses if indicated clinically. Within

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the elective and emergency groups, patients randomly received either bupivacaine plain solution or bupivacaine with adrenaline 1 in 200000. The elective group had received no previous extradural analgesia, whereas in the emergency group all had received previously extradural plain bupivacaine during labour.

At delivery of the infant, a length of umbilical cord was isolated between clamps and samples of umbilical venous (UV) and umbilical arterial (UA) blood were obtained. Maternal venous blood (MV) was sampled also at delivery. Plasma bupivacaine concentrations were measured by a modification of the method of Reynolds and Beckett [12] with the ethyl homologue of bupivacaine as internal standard. Plasma and standard were alkalinized and extracted into ether, back extracted into hydrochloric acid and re-extracted into ether, which was concentrated by boiling, to approximately 10 µl. A 3-µl sample was analysed by gas chromatography using 3% OV17 on AW Chromasorb WHP at the stationary phase, and a nitrogen detector.

Data were analysed using the SAS statistical package on the Amdahl V8 computer at the University of London Computer Centre. Differences between groups were tested by analysis of variance and Student's t test. The relationship of bupivacaine concentration and concentration ratios with time intervals was examined with Pearson and Spearman rank correlation. Results with $P < 0.05$ were considered significant.

RESULTS

Maternal age, weight and infant weight were not significantly different between the elective groups given plain or adrenaline solutions or the emergency groups given plain or adrenaline solutions (table I).

The modal dose of bupivacaine for Caesarean section in all four groups was 100 mg. The dose of bupivacaine for labour analgesia before emergency Caesarean section was 121 (80) mg (mean (SD)) in the plain group and 113 (70) mg in the adrenaline group. Further details of these doses and the time course of maternal plasma concentrations of bupivacaine have been reported separately [11].

Plasma concentrations of bupivacaine (MV, UV and UA) were significantly greater ($P < 0.0001$) in the emergency groups than in the elective groups (table II). Adrenaline was not associated with significant changes in plasma concentrations of local anaesthetic in MV, UV or UA.

Plasma concentrations of bupivacaine in MV increased significantly with the total dose (mg kg^{-1}) administered in the plain, adrenaline, elective ($P < 0.0001$) and emergency groups ($P < 0.03$).

The effect of time on maternal and fetal plasma concentrations of bupivacaine was investigated also. There were significant positive correlations for first dose to delivery interval (FDD) with MV, UV and UA, reflecting total dose (table III). In contrast, there were mostly negative correlations for last dose to delivery interval (LDD) with MV and UV and no significant correlation with UA (table IV).

Bupivacaine concentration ratios were greater in the emergency group compared with the elective group, but this difference was significant ($P < 0.04$) only for the UV:MV ratio. Adrenaline had no significant effect on UV:MV or UA:MV but in the elective group was associated with greater UA:UV ratios ($P < 0.01$) (table V).

In eight cases (table VI), the UA:UV ratio was substantially greater than 1. All of these mothers had received extradural adrenaline, and delivery occurred within 40–52 min of the last dose (fig. 1).

TABLE I. *Clinical data (mean (SD))*

	Elective		Emergency	
	Plain ($n = 20$)	Adrenaline ($n = 20$)	Plain ($n = 20$)	Adrenaline ($n = 20$)
Maternal age (yr)	31.0 (6.7)	28.9 (5.8)	30.2 (4.4)	30.7 (4.7)
Maternal wt (kg)	76.3 (15.8)	72.0 (8.6)	74.6 (14.1)	76.0 (11.8)
Infant wt (kg)	3.05 (0.66)	3.04 (0.67)	3.53 (0.36)	3.28 (0.85)
Gestation (weeks)	37.9 (2.2)	38.8 (2.3)	40.0 (1.3)	39.3 (3.1)
Total dose of bupivacaine (mg kg^{-1})	1.6 (0.61)	1.5 (0.3)	3.0 (0.8)	2.9 (1.1)

TABLE II. *Bupivacaine concentrations ($\mu g\ ml^{-1}$) (mean (SD))*

	Elective	Emergency	All	Range
Maternal vein				
Plain	0.644 (0.378) ($n = 20$)	0.915 (0.273) ($n = 20$)	0.779 (0.353)	0.190–1.97
With adrenaline	0.513 (0.118) ($n = 19$)	0.862 (0.223) ($n = 19$)	0.688 (0.250)	0.351–1.35
All	0.580 (0.287)	0.889 (0.248)	0.735 (0.309)	
Range	0.190–1.970	0.449–1.590		
Umbilical vein				
Plain	0.187 (0.083) ($n = 19$)	0.326 (0.145) ($n = 20$)	0.258 (0.137)	0.076–0.645
With adrenaline	0.168 (0.074) ($n = 20$)	0.318 (0.154) ($n = 20$)	0.243 (0.141)	0.063–0.76
All	0.177 (0.078)	0.322 (0.148)	0.250 (0.138)	
Range	0.063–0.344	0.081–0.760		
Umbilical artery				
Plain	0.138 (0.060) ($n = 17$)	0.286 (0.151) ($n = 19$)	0.216 (0.138)	0.017–0.662
With adrenaline	0.177 (0.108) ($n = 20$)	0.287 (0.116) ($n = 17$)	0.227 (0.124)	0.052–0.513
All	0.159 (0.090)	0.287 (0.133)	0.222 (0.130)	
Range	0.017–0.513	0.119–0.662		

TABLE III. *Pearson correlations of plasma bupivacaine concentration for first dose to delivery interval (FDD)*

	Elective	Emergency	All
Maternal vein			
Plain	0.66 ($P < 0.002$)	−0.04 (ns)	0.32 ($P < 0.05$)
With adrenaline	−0.08 (ns)	0.13 (ns)	0.59 ($P < 0.0001$)
All	0.62 ($P < 0.0001$)	0.05 (ns)	0.43 ($P < 0.0001$)
Umbilical vein			
Plain	0.63 ($P < 0.004$)	−0.018 (ns)	0.34 ($P < 0.04$)
With adrenaline	0.23 (ns)	0.002 (ns)	0.41 ($P < 0.009$)
All	0.50 ($P < 0.002$)	−0.08 (ns)	0.38 ($P < 0.001$)
Umbilical artery			
Plain	0.03 (ns)	0.01 (ns)	0.43 ($P < 0.01$)
With adrenaline	0.34 (ns)	0.21 (ns)	0.44 ($P < 0.007$)
All	0.04 (ns)	0.09 (ns)	0.43 ($P < 0.001$)

TABLE IV. *Pearson correlations of plasma bupivacaine concentrations for last dose to delivery interval (LDD)*

	Elective	Emergency	All
Maternal vein			
Plain	−0.25 (ns)	−0.28 (ns)	−0.26 (ns)
With adrenaline	−0.67 (ns)	−0.41 (ns)	−0.65 (ns)
All	−0.33 ($P < 0.04$)	−0.30 (ns)	−0.39 ($P < 0.0005$)
Umbilical vein			
Plain	−0.46 ($P < 0.05$)	−0.15 (ns)	−0.28 (ns)
With adrenaline	−0.40 (ns)	−0.19 (ns)	−0.44 ($P < 0.005$)
All	−0.44 ($P < 0.006$)	−0.16 (ns)	−0.35 ($P < 0.002$)
Umbilical artery			
Plain	−0.28 (ns)	−0.02 (ns)	−0.15 (ns)
With adrenaline	0.09 (ns)	0.26 (ns)	−0.08 (ns)
All	−0.02 (ns)	0.07 (ns)	−0.12 (ns)

TABLE V. *Bupivacaine concentration ratios (mean (SD)). UV = Umbilical vein; MV = maternal vein; UA = umbilical artery*

	Elective	Emergency	All
UV:MV			
Plain	0.31 (0.12) ($n = 19$)	0.37 (0.14) ($n = 20$)	0.34 (0.14)
With adrenaline	0.32 (0.10) ($n = 19$)	0.39 (0.15) ($n = 19$)	0.35 (0.13)
All	0.31 (0.11)	0.38 (0.14)	0.35 (0.13)
UA:MV			
Plain	0.23 (0.10) ($n = 17$)	0.32 (0.14) ($n = 19$)	0.28 (0.13)
With adrenaline	0.31 (0.16) ($n = 19$)	0.36 (0.14) ($n = 16$)	0.33 (0.15)
All	0.28 (0.14)	0.34 (0.14)	0.31 (0.14)
UA:UV			
Plain	0.74 (0.22) ($n = 17$)	0.87 (0.16) ($n = 19$)	0.81 (0.20)
With adrenaline	1.10 (0.44) ($n = 20$)	1.10 (0.41) ($n = 17$)	1.10 (0.42)
All	0.91 (0.38)	0.95 (0.31)	0.93 (0.35)

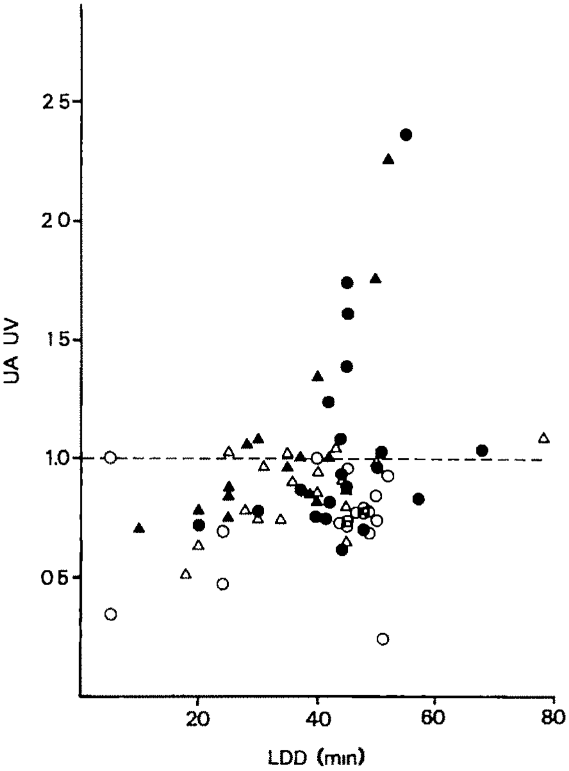

FIG. 1. Umbilical arterial:umbilical venous bupivacaine concentration ratios (UA:UV) plotted against last dose to delivery interval (LDD). Points above UA:UV ratio of 1.0 indicate back-transfer ○ = Elective plain; ● = elective adrenaline; △ = emergency plain, ▲ = emergency adrenaline.

There was no significant correlation between any ratios (UV:MV, UA:MV, UA:UV) and duration of extradural blockade as measured by FDD. In contrast, there were significant correlations between some of the ratios and LDD. The UA:UV ratio correlated significantly with LDD in the emergency group ($r = 0.455$; $P < 0.01$) and both adrenaline sub-groups.

The UV:MV ratio showed a negative correlation with LDD in all groups but was significant only in the elective plain group ($r = -0.504$; $P < 0.03$). For UA:MV and LDD, there was no overall correlation, although there was a negative correlation in the elective plain group ($r = -0.561$; $P < 0.02$) and a positive correlation in the emergency adrenaline group ($r = 0.593$; $P < 0.02$).

DISCUSSION

In this study, plasma concentrations of bupivacaine in MV increased significantly with the total dose of drug (mg kg^{-1}) administered. This is consistent with previous findings [2, 11] that maternal maximum concentration correlates with total dose but not with dose rate, and reflects the fact that, with continuous administration at a constant rate, plasma concentration of a drug increases for four to seven half-lives and only the plateau concentration reflects dose rate. As the elimination half-life of bupivacaine in parturients is 6 h [13] to 9 h [14, 15], plasma concentrations

TABLE VI. *The eight patients in whom UA : UV ratios were substantially greater than 1. All received extradural adrenaline*

	Total dose of bupivacaine (mg kg^{-1})	LDD (min)	MV ($\mu g\ ml^{-1}$)	UA ($\mu g\ ml^{-1}$)	UV ($\mu g\ ml^{-1}$)	UA:UV
Elective	1.51	42	0.394	0.193	0.154	1.25
	1.33	45	0.410	0.297	0.184	1.61
	1.56	45	0.420	0.106	0.076	1.40
	1.75	55	0.516	0.513	0.217	2.36
	1.43	45	0.476	0.270	0.155	1.74
Emergency	2.74	50	0.920	0.492	0.279	1.76
	2.41	52	0.470	0.184	0.081	2.27
	2.16	40	0.629	0.233	0.173	1.35

are unlikely to plateau during the course of an obstetric extradural block.

Transplacental distribution of bupivacaine has been investigated in animals [16–19] by methods that are not applicable to humans. Simultaneous sampling of fetal and maternal blood at delivery is relatively simple in humans, but examines only one moment in a continuous process. We have attempted to overcome this problem by using subjects who received bupivacaine for varying periods of time.

Simultaneous concentrations of bupivacaine in UV, UA and MV have rarely been reported [20]. UV:MV ratios on initial administration are an index of placental transfer rate, and while fetal tissue saturation is incomplete, UA:MV bupivacaine concentration ratio should increase with time to reach a plateau which approaches the UV:MV ratio, although during maternal drug absorption a small gradient may persist if there is fetal drug metabolism. However, both UV:MV and UA:MV ratios are affected by transplacental pH gradient [21,22] and are governed principally by the gradient of α_1-acid glycoprotein [23,24]. This major cause of interindividual variation should be overcome by examining UA:UV ratios, which gauge the extent of fetal equilibration and the direction of placental transfer but are independent of transplacental α_1-acid glycoprotein gradient.

In this study, UA:UV increased significantly with LDD but not with FDD, which suggests that equilibration occurred during each dosage interval in approximately 30 min (fig. 1). The negative relationship between UV:MV and time suggests that bupivacaine approached equilibrium across the placenta in a single circulation, while equilibration in the whole fetal compartment took less than 1 h, and in some cases reverse transfer occurred.

The eight UA:UV ratios markedly in excess of 1 (fig. 1, table VI) were unexpected. All occurred in patients receiving extradural adrenaline and within an LDD of 40–55 min. In five of these patients, relatively low maternal concentrations were clearly promoting reverse placental transfer. The phenomenon of back transfer has been reported previously [16], although not in association with adrenaline. The infants at birth did not appear more acidotic than the others. Differences in fetal and maternal protein binding may play a role in this phenomenon, while maternal α_1-acid glycoprotein concentration may increase during stress [25].

UV:MV and UA:MV ratios were of the same order of magnitude and did not appear to approach unity with time. There is thus no evidence from the present study or recent animal work [17,18] that high fetal tissue uptake of bupivacaine is the principal cause of low F:M ratios. Low equilibrium F:M ratios of bupivacaine may be explained by the reduced protein binding of bupivacaine in fetuses. This has been recorded consistently in man and rabbits [24, 26–28] and is related to the small concentrations of α_1-acid glycoprotein in fetal blood [23,24,29]. The effect of pH on equilibrium F:M ratios has been well documented by others [21,22], and was not studied therefore in the present series.

As reported previously [1], the use of extradural adrenaline was associated with higher F:M ratios, but this finding, although barely significant, would appear to be related more to UA:MV and UA:UV ratios than to UV:MV and was dependent upon the eight aberrant cases. Adrenaline was, therefore, not affecting placental transfer rate and in eight patients was associated with reverse transfer. This observation might in part reflect less fluctuation in maternal concentration, which would otherwise peak at or near delivery.

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EVALUATION OF "3 IN 1" LUMBAR PLEXUS BLOCK IN PATIENTS HAVING MUSCLE BIOPSY

T. H. MADEJ, F. R. ELLIS AND P. J. HALSALL

SUMMARY

Winnie and co-workers described a technique of blocking the lateral cutaneous nerve of thigh, femoral and obturator nerves using one injection of local anaesthetic into the fibrous sheath surrounding the femoral nerve. We studied 40 patients undergoing biopsy of vastus medialis for investigation of malignant hyperpyrexia, for onset, quality and recovery from this block. The patients were assigned in a random double-blind fashion to receive 0.6 ml kg^{-1} of one of two anaesthetic solutions: 1% lignocaine with 1 in 100000 noradrenaline or 0.25% bupivacaine. Bupivacaine produced a similar onset time but longer duration of action compared with lignocaine. Median peak plasma concentrations of six patients in each group did not approach values associated with toxicity. This study demonstrated a 12.5% and 87.5% partial and complete femoral nerve block, respectively, and a 67.5% success rate for lateral cutaneous nerve of thigh using Winnie's technique. There was no clinical evidence of obturator nerve block.

Winnie, Ramamurthy and Durrani [1] first described a technique of blocking the lateral cutaneous nerve of thigh, the femoral nerve and the obturator nerve using one injection of local anaesthetic into the compartment formed by the fibrous sheath surrounding the femoral nerve. While technically easier than blocking each nerve individually, this method reduces the number of needle insertions and also the total volume of local anaesthetic required.

Patients presenting for muscle biopsy for investigation of malignant hyperpyrexia (MH) pose special problems for the anaesthetist, as many anaesthetic drugs may trigger the hypermetabolic response. A technique using local anaesthesia with additional sedation when necessary may be useful for these patients [2]. The biopsies are taken from the vastus medialis muscle through a 5-cm incision. A standardized procedure and the absence of major trauma make this an ideal model for studying the onset, quality and duration of a nerve block. In the Leeds University MH Investigation Unit at St James's University Hospital, "3 in 1" blocks have been performed for muscle biopsy using bupivacaine. Lignocaine was expected to give a faster onset and bupivacaine a longer duration of action. However, it was not known which offered advantages for peroperative or postoperative analgesia. The present study was designed to evaluate Winnie and co-workers' technique for 3 in 1 lumbar plexus block and to compare the efficacy, speed of onset and duration of lignocaine and bupivacaine.

PATIENTS AND METHODS

Forty ASA I or II patients (aged 20–72 yr) undergoing vastus medialis muscle biopsy consented to take part in the study. They were allocated randomly to receive either bupivacaine or lignocaine. When the patient arrived in the anaesthetic room, baseline arterial pressure and heart rate were recorded and measurements were repeated at 5-min intervals for 30 min after performing the 3 in 1 block. A cannula was inserted into a vein and, in six patients in each local anaesthetic group, venous blood samples were taken at 5, 10, 20, 30, 45, 60 and 120 min after administration of the block. Plasma was stored at −20 °C and analysed using high pressure liquid chromatography (HPLC) with a coefficient of variation of 4%.

The technique for 3 in 1 block, as described by Winnie and co-workers, was used, with a needle

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and extension tubing. When paraesthesiae in the distribution of the femoral nerve were elicited, 0.6 ml kg^{-1} of local anaesthetic was injected, to a maximum of 40 ml, with pressure applied distal to the point of injection across the femoral canal to prevent distal spread of local anaesthetic. The local anaesthetic, 1.0% lignocaine with 1 in 100000 noradrenaline or 0.25% bupivacaine according to a randomization table, was drawn up by an anaesthetist who did not take part in the assessments.

Following baseline measurements, the time of onset of anaesthesia was assessed at 5-min intervals after injection until anaesthesia was complete, or for 30 min. Recovery was assessed hourly: straight leg raising was scored in degrees and cutaneous cold sensation was tested in three areas, the lateral, ventral and medial aspect of the thigh. Patients scored pain during and after operation, using verbal and visual analogue scores [3]. If anaesthesia was inadequate for surgery at 30 min it was supplemented with local anaesthetic to the skin and i.v. sedation (fentanyl and Diazemuls). Postoperative analgesia was given on request as paracetamol 1 g by mouth up to 6-hourly.

Statistical comparisons were made using Student's t test (unpaired) for parametric data and Chi-squared and Fisher's exact test for non-parametric data.

RESULTS

The sex distribution, mean age, height and weight of patients in the two groups were similar (table I). There were small, clinically insignificant, changes in arterial pressure and heart rate in both groups. The median (range) peak plasma concentration after lignocaine was 1.85 (1.22–4.42) μg ml^{-1} and after bupivacaine 0.67 (0.35–0.80) μg ml^{-1}. The median (range) time to peak plasma concentration was 37.5 (5–60) min after lignocaine and 37.5 (10–60) min after bupivacaine (table II).

At 5 min after injection there was some evidence of anaesthesia in all but five patients (three received lignocaine, two bupivacaine). The maximum effect was not seen until 30 min had elapsed in 11 patients (three received lignocaine, eight bupivacaine) and the median (range) time to maximum effect in both groups was 20.5 (5–120) min. Eight patients in each group complained of discomfort during operation. Similar numbers in each group (one bupivacaine, three lignocaine) received supplementary medication during operation. Recovery of motor and sensory block was faster after lignocaine compared with bupivacaine (median (range) 4 (1–9) and 6 (3–9) *v.* 17 (4–24) and 23 (12–52) h, respectively) ($P < 0.05$). Eight patients complained of postoperative pain ($P < 0.01$) and four received postoperative analgesia in the lignocaine group, compared with none in the bupivacaine group.

TABLE I. *Demographic data (ratio or mean (SD))*

	Lignocaine	Bupivacaine
Sex (M.F)	11:9	11:9
Age (yr)	41.5 (15)	39.5 (15)
Height (m)	1.64 (0.10)	1.75 (0.07)
Weight (kg)	70 (15)	76 (15)

TABLE II. *Median (range) peak plasma concentration (Cmax) and time of peak plasma concentration (Tmax)*

	Lignocaine ($n = 6$)	Bupivacaine ($n = 6$)
Cmax (μg ml^{-1})	1.85 (1.22–4.42)	0.67 (0.35–0.80)
Tmax (min)	37.5 (5–60)	37.5 (10–60)

All patients had loss of sensation on the medial aspect of the thigh and this was the most common ($P < 0.05$) initial evidence of nerve block. More than 90% of patients had loss of sensation on the ventral aspect of the thigh and this was the first evidence of nerve block in 12.5% of patients. In 20% of patients loss of sensation was detected simultaneously on the medial and ventral aspects of the thigh. Loss of sensation on the lateral aspect of the thigh occurred in 67.5% of patients; this was significantly less common ($P < 0.05$) than other sensory changes (table III). One patient in each group had loss of sensation in all three areas at 5 min after injection. Absence or weakness of knee extension was found in 87.5% of patients.

TABLE III. *Number of patients with loss of sensation on the medial, ventral and lateral aspect of the thigh and weakness of knee extension. * Lower incidence* ($P < 0.05$) *compared with other sensory changes (Fisher's Exact test)*

	Lignocaine ($n = 20$)	Bupivacaine ($n = 20$)
Medial	20	20
Ventral	19	18
Lateral	13*	14*
Knee extension	17	18

DISCUSSION

We used lignocaine solution with a vasoconstrictor in order to avoid toxic doses when using doses equipotent with bupivacaine. Noradrenaline was used in preference to adrenaline in order to avoid beta receptor stimulation in MH patients.

None of the patients having venous blood sampling had additional local anaesthetic after the 3 in 1 block. Median peak plasma concentrations did not approach the threshold for CNS toxicity in man (5–10 $\mu g\ ml^{-1}$ for lignocaine and 2–4 $\mu g\ ml^{-1}$ for bupivacaine) [4]. Injection of local anaesthetic around the femoral and sciatic nerve or brachial plexus results in a low rate of systemic absorption compared with other sites of injection [5, 6]. It could be argued that the maximum permitted dose of local anaesthetic should be related to the site of injection to enable combined lower limb blocks to be used [7]. A peak of 4.42 $\mu g\ ml^{-1}$ at 5 min after injection in one patient receiving lignocaine suggested rapid intravascular absorption despite a negative aspiration for blood, and this emphasizes the need for vigilance, irrespective of the site of injection.

The duration of action of bupivacaine was longer than that of lignocaine, despite the addition of noradrenaline to the latter. Timing and pattern of onset were similar for both drugs. The most frequent first sign of nerve block was loss of sensation on the medial aspect of the thigh. As the obturator nerve lies distant from the point of injection, it must be assumed that the area tested was supplied by the femoral rather than the obturator nerve. This was confirmed by the fact that three patients had sensory loss restricted to this area, and it is inconceivable that the obturator nerve alone could be blocked with this technique.

The femoral nerve divides just below the inguinal ligament, with the saphenous and medial cutaneous nerve of thigh lying medial to the intermediate cutaneous nerve of thigh and muscular branches to quadratus femoris. If the needle were to be placed too distally and medially, a partial femoral nerve block could result and even cause paraesthesiae before injection. The use of a nerve stimulator to detect quadriceps contraction at low current output ensures needle placement in close proximity to the main body of the femoral nerve.

Loss of sensation on the lateral aspect of the thigh from block of the lateral cutaneous nerve of thigh was usually late in onset, but did develop in 67.5% of patients. These were the only blocks with good evidence of spread of local anaesthetic solution to involve a nerve other than the main trunk or branches of the femoral nerve.

There was no evidence from this study of obturator nerve block such as weakness of thigh abduction. However, the obturator is a difficult nerve to assess, as the cutaneous distribution has variable overlap with the medial cutaneous branch of the femoral nerve, and the adductor muscles are also supplied by the sciatic nerve. Thus in our experience the block as described by Winnie and co-workers could be described more accurately as an "extended femoral nerve block" rather than a lumbar plexus block.

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INCIDENCE OF ARRHYTHMIAS IN DENTAL ANAESTHESIA: A CROSS-OVER COMPARISON OF HALOTHANE AND ISOFLURANE

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SUMMARY

Fifty patients received halothane anaesthesia during the surgical removal of 3rd molars from one side of the mouth and isoflurane during extractions on the other. Degree of surgical difficulty was matched, and end-tidal P_{CO_2} *did not differ significantly between sides. A significantly higher incidence of arrhythmias occurred during halothane, compared with isoflurane, anaesthesia. This difference occurred primarily when halothane was given for the first operated side. A clinically important feature of the stability of cardiac rhythm during isoflurane anaesthesia was demonstrated—when frequent ectopic beats occur during halothane anaesthesia, a significant decrease in the rate of premature contractions occurs within 3 min of discontinuing halothane and introducing isoflurane.*

Dental extractions under general anaesthesia are associated with a significant incidence of cardiac arrhythmias [1,2]. The incidence is particularly high during halothane anaesthesia [3,4].

Isoflurane is known to sensitize the myocardium to adrenaline to a lesser extent than halothane [5], and stability of cardiac rhythm with isoflurane anaesthesia has been demonstrated in patients undergoing a variety of procedures [6,7].

The use of isoflurane to minimize arrhythmias in dental anaesthesia has been investigated in both children [8] and adults [9,10]. These studies involved randomly assigning patients to receive one or another inhalation agent during dental extraction. Two of the studies [8,9] made no note of which teeth were extracted, and none has matched the difficulty or duration of extraction.

This study was designed to match both the stimuli causing arrhythmias and the patient susceptibility to these stimuli. In addition, the study was designed to investigate the authors' clinical impression that, if ventricular arrhythmias occurred during halothane anaesthesia, a change to isoflurane often resulted in a very rapid decrease in the frequency of ectopic beats.

PATIENTS AND METHODS

We studied 50 patients (ASA I), scheduled for routine surgical removal of bilateral lower 3rd molars (with or without upper 3rd molars). An additional criterion for admission was that the lower 3rd molars were impacted symmetrically, so that the dental surgeon anticipated equal amounts of surgical stimulation on each operated side.

Patients gave informed consent and the study was approved by the local Ethics Committee.

No premedication was given. Anaesthesia was induced with thiopentone 4.5–5.5 mg kg^{-1} i.v. and, following suxamethonium 1 mg kg^{-1} i.v., the trachea was intubated with an uncuffed nasal tube and the throat was packed. The lungs were ventilated manually via a Bain circuit with 66% nitrous oxide in oxygen at a fresh gas flow of 9 litre min^{-1} and gradually increasing concentrations of halothane (up to 4%) until the resumption of spontaneous ventilation.

At this point, patients were transferred into the operating theatre. Anaesthesia was maintained via a Bain circuit with 66% nitrous oxide in oxygen and, initially, either 1.5% halothane or 2% isoflurane.

Each patient received halothane during the

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removal of teeth from one side of the jaw, and isoflurane during extractions from the opposite side. The order in which the agents were used was randomized. The first agent was introduced as soon as the patients arrived in theatre. The change to the second agent was made as soon as final suturing began on the first side.

ECG and end-tidal partial pressure of carbon dioxide ($P\text{E}'_{\text{CO}_2}$) were displayed continuously. $P\text{E}'_{\text{CO}_2}$ was recorded every 2 min, and a mean $P\text{E}'_{\text{CO}_2}$ for each operated side was calculated. Arterial pressure was recorded automatically every 2 min. In addition, a single channel ECG recording was made on cassette tape, using an Oxford Medilog 2-24 recorder, for later analysis.

An event log was kept, indicating the times of first incision and final stitching on each operated side. The cassette tapes and this event log were subsequently submitted to analysis using a Reynolds Pathfinder II ECG analyser, the operator being unaware of the order in which the anaesthetic agents had been used. The number of supraventricular premature beats (SVPB) and ventricular premature beats (VPB) were recorded for each operated side, together with the average heart rate for that period.

Results were analysed using Student's *t* test or analysis of variance for data which were normally distributed, and the paired Wilcoxon test for data relating to premature contractions, which did not follow a normal distribution.

RESULTS

We studied 50 patients (12 males) with a mean age of 22.8 yr (SD 4.37). Group HI ($n = 25$) received halothane anaesthesia for the first operated side, and isoflurane for the second. Group IH ($n = 25$) received the agents in reverse order. Data for each operated side in both groups are summarized in tables I and II.

TABLE I *Data (mean (SD)) for the 25 patients who received isoflurane anaesthesia for the first operated side, and halothane for the second (group IH)*

	Side one (isoflurane)	Side two (halothane)
Age (yr)	22.32 (4.07)	
Heart rate (beat min^{-1})	99.4 (23 09)	98.76 (22.17)
Duration (min)	8.36 (4.60)	7.68 (4.21)
$P\text{E}'_{\text{CO}_2}$ (kPa)	5.31 (0 74)	5.30 (0.71)
Delay between sides (min)	2 16 (1.46)	

Analysis of variance revealed no significant differences between operated sides or between groups, for mean heart rate, duration of surgery or mean end-tidal carbon dioxide concentration. There was no significant difference in age between the two groups. The delay between sides (closure on side one to incision on side two) did not differ significantly (Student's *t* test).

For initial analysis of the incidence of premature beats, the data from all 50 patients were pooled, either to compare halothane with isoflurane (irrespective of the side for which the agent was administered) or to compare the first and second operated sides (irrespective of which agent was administered). A significantly higher incidence of SVPB and VPB occurred during halothane administration compared with isoflurane. There was also a similarly high and significant incidence of premature beats on the first operated side compared with the second (table III).

The reason for this disparity was demonstrated when the ectopic rates in groups IH and HI were examined separately (table IV). A significantly higher incidence of both SVPB and VPB occurred

TABLE II. *Data (mean (SD)) for the 25 patients who received halothane anaesthesia for the first operated side, and isoflurane for the second (group HI)*

	Side one (halothane)	Side two (isoflurane)
Age (yr)	23.28 (4.69)	
Heart rate (beat min^{-1})	91.60 (17.36)	92.96 (16.76)
Duration (min)	7.76 (3 03)	8 96 (5 07)
$P\text{E}'_{\text{CO}_2}$ (kPa)	5.54 (0.76)	5.57 (0.78)
Delay between sides (min)	2.72 (1.93)	

TABLE III. *Incidence of premature beats (mean (SD)) according to agent used and to operated side. Significance testing is by paired Wilcoxon test*

	Halothane	Isoflurane	*P*
SVPB (min^{-1})	0 52 (2.33)	0.24 (1.12)	< 0.01
VPB (min^{-1})	3.10 (10.39)	0.09 (0.21)	< 0.025
	Side one	Side two	
SVPB (min^{-1})	0.51 (2.33)	0.24 (1.12)	< 0 05
VPB (min^{-1})	3.13 (10.39)	0.05 (0 11)	< 0.005

TABLE IV. *Incidence of premature beats (mean (SD)) in groups IH and HI Significance testing is by paired Wilcoxon test*

	Side one	Side two	*P*
Group IH			
SVPB (min^{-1})	0.02 (0.06)	0.03 (0.09)	ns
VPB (min^{-1})	0.10 (0 28)	0.04 (0.11)	ns
Group HI			
SVPB (min^{-1})	1.00 (3.25)	0.46 (1.57)	< 0 05
VPB (min^{-1})	6.16 (14.18)	0.07 (0.12)	< 0 005

TABLE V. *Frequency of SVPB and VPB*

	Halothane	Isoflurane
SVPB ⩾ 1 min	5	2
SVPB < 1 min	45	48
VPB ⩾ 1 min	8	2
VPB < 1 min	42	48

in group HI during halothane administration compared with isoflurane. No analogous difference occurred in group IH. The premature contraction rates in both operated sides of group IH and in the isoflurane side of group HI were similar.

The difference in incidence of arrhythmias resulted almost entirely from the high rate of premature contractions in those patients receiving halothane during surgery on the first side. Arrhythmias were not distributed uniformly; the majority of patients had few arrhythmias (less than one premature beat per minute), while a few patients had a high incidence (table V).

There were no significant correlations between the incidence of SVPB or VPB and patient age, heart rate or PE'_{CO_2}.

DISCUSSION

By matching patient, surgical stimulus and PE'_{CO_2}, any difference in the incidence of arrhythmias noted in the study can be ascribed with confidence to the difference in anaesthetic agent administered. We found that there was no difference in heart rate between patients receiving isoflurane and halothane, in contrast to the more rapid rate with isoflurane noted in previous studies [8–10]. This discrepancy may be a result of some admixture of agents that occurred inevitably in this study.

It was considered unethical to allow a prolonged period of anaesthetic washout and washin between agents. It was, therefore, inevitable that patients receiving one agent would have possessed a significant blood concentration of the alternative agent after the changeover. While this situation is not ideal, it was accepted for two reasons in addition to the ethical problems of unnecessarily prolonged anaesthesia.

(a) Admixture would tend only to obscure differences between agents; the risk was of a false negative result.

(b) Previous clinical experience had suggested that, if arrhythmias occurred during halothane anaesthesia, a change to isoflurane would often result in cessation or diminution of the arrhythmias within a few minutes. It was anticipated, therefore, that a study designed in this manner could detect differences between these two agents, and that the results of the study would be relevant to clinical practice.

Significant differences between agents were detected in group HI, with a 100-fold decrease in the incidence of VPB and a two-fold decrease in the incidence of SVPB on changing from halothane to isoflurane. No such differences were detected in group IH, who received isoflurane as the agent for the first operated side. Indeed, group IH and the isoflurane side of group HI appeared to exhibit a similar incidence of premature beats.

This asymmetry in results may be explained by differences in the characteristics of the agents used. Isoflurane is less soluble than halothane, and therefore has a shorter washin period [11]. As a result, its blood concentration should increase rapidly to a plateau and remain relatively constant throughout the period of use on either operated side.

In group HI, halothane should also be present in relatively constant blood concentrations during surgery, because concentrations were increased rapidly by "overpressure" during induction. In contrast, in group IH the concentration of halothane increased slowly, as overpressure was not used, and this relatively low concentration for part of the period of surgery in group IH may account for the low incidence of premature contractions observed when halothane was used for the second operated side. It was demonstrated in group HI, however, that when premature contractions (especially those of ventricular origin) occurred during halothane anaesthesia, a change to isoflurane improved cardiac rhythm, despite recurring surgical stimulation. In this study, this improvement became evident within a mean 2.72 min—a period which is short enough to be clinically useful.

The ideal solution to the problem of premature beats during dental surgery under general anaesthesia may be to administer isoflurane to every patient, especially as its short washout time [11] should result in rapid recovery from anaesthesia (although some investigators have found no advantage over halothane in this respect, in paediatric dental practice [8,12]).

The increased incidence of arrhythmias during halothane anaesthesia resulted from a high incidence in a small group of patients—the majority of patients having an acceptably low rate of premature beats (table V). On this basis, halothane might be administered to all patients initially. Only in those patients in whom an unacceptably high rate of premature contractions developed would a change to isoflurane be advisable, in the expectation that a decline in the rate of ectopic beats would occur within a few minutes.

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AUDITORY EVOKED POTENTIALS DURING PROPOFOL ANAESTHESIA IN MAN

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Sensory-evoked potentials are the electrophysiological responses of the nervous system to sensory stimulations. Thus auditory evoked potentials in wave forms represent specific responses to auditory stimulation [1]. The first waves (I–V) represent activity originating from the brainstem (brainstem auditory evoked potentials (BAEP)) while Pa, Nb waves represent the early cortical response (or middle latency responses (MLR)).

Previous reports have demonstrated the potential value of intraoperative BAEP monitoring during posterior fossa surgery [2]. Intraoperative alteration in BAEP may result from impairment of nervous or vascular structures or from specific drug effects [3]. Thus it is important to differentiate between changes in BAEP that may occur as a result of ischaemia or compression of the neural structures and those produced by drugs used in anaesthesia. Previous studies have demonstrated that enflurane [4], halothane [5] and etomidate [6] produce graded changes on MLR while Althesin [7] and etomidate [6] do not affect the brainstem response.

Propofol is a useful drug for induction and maintenance of hypnosis during total i.v. anaesthesia [8, 9]. Its fast distribution and rapid metabolism result in a short plasma half-life and this indicates that the drug may be suitable for anaesthesia during neurosurgical procedures [10]. The aim of this study was to examine the effect of propofol on BAEP monitoring in surgical patients.

SUMMARY

The effects of propofol on auditory evoked potentials were studied in nine patients undergoing otorhinolaryngology surgery. After recording of basal evoked potentials patients received propofol 2 mg kg^{-1} over 2–3 min for induction of anaesthesia. Potentials were recorded every 10 min (T1, T2, T3). During T1, T2, T3, the infusion rates of propofol for maintenance of anaesthesia were respectively 7, 5 and 3 mg kg^{-1} h^{-1} consecutively. Middle latency component was affected markedly. Brainstem waves latencies I, III, V were increased significantly, while amplitude waves I, III, V remained constant.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee. Following informed consent we studied nine adult patients (five male) (mean age 31 yr (range 21–63 yr); mean weight 65 kg (range 53–85 kg)) scheduled for elective ENT surgery (three tonsillectomy, four rhinoseptoplasty, two removals of parotid gland). All patients were evaluated before operation by an anaesthetist and an otorhinolaryngologist.

All patients were ASA I and preoperative audiograms did not show any hearing deficit.

Anaesthesia

Premedication comprised hydroxyzine 100 mg and chlorazepate 1 mg kg^{-1} 2 h before anaesthesia.

Following baseline measurements of systolic, diastolic and mean arterial pressures (Dinamap) and central temperature (deep body thermometer, Cambridge, England), anaesthesia was induced with propofol 2 mg kg^{-1} i.v. over 2–3 min followed by vecuronium 0.1 mg kg^{-1} i.v., all given

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through an antecubital vein. The patient breathed 100% oxygen whilst spontaneous ventilation was maintained, but when apnoea occurred the lungs were ventilated mechanically ($F\text{I}_{O_2} = 1$) after tracheal intubation. Anaesthesia was maintained with only the propofol infusion. The rate of infusion was first kept constant at 7 mg kg^{-1} h^{-1} (T1), then decreased to 5 mg kg^{-1} h^{-1} (T2) and finally to 3 mg kg^{-1} h^{-1} (T3). Each step was maintained 10 min. Arterial pressure, temperature and end-tidal concentration of carbon dioxide ($P\text{E}'_{CO_2}$) (Engstrom Eliza, Gambro, Sweden) were monitored during the study. $P\text{E}'_{CO_2}$ was kept constant by adjusting the minute ventilation and the temperature using a warming blanket (Heto, Birteröd, Denmark).

At the end of each period, venous blood samples were collected from the arm opposite to that receiving the infusion for measurement of propofol concentrations. Propofol concentrations in whole blood samples were measured following extraction into cyclohexane, by high pressure liquid chromatography (Ultrasphere C18. Altex) using spectrofluorimetric detection (λ excitation 276 nm; λ emission 310 nm). The limit of sensitivity of the assay was 5 μg ml^{-1} and the coefficient of variation over the concentration range measured was approximately 5%.

Recording the auditory evoked potential [11]

BAEP were recorded from vertex (CZ) with reference to the right or left ear lobes (A1 or A2) using silver–silver chloride disc electrodes. The evoked potentials were recorded when the patient arrived in the anaesthesia room (basal) and at the end of each period (T1, T2, T3). Electrode impedances were maintained at less than 3 kΩ. Monaural auditory clicks (duration 0.1 ms, rate 10 Hz) were delivered at an intensity of 60 dB above the patient's hearing threshold with contralateral masking at 40 dB. The signals were filtered between 300 and 3000 Hz. For each run 2048 sweeps were averaged (Nihon-Kohden neuropack II-plus, Tokyo, Japan).

In six patients, for MLR recording, we used stimuli of 0.1 ms duration at 5 Hz frequency with 5–1000 Hz filters; 512 sweeps were averaged.

TABLE I. *Values for I, III, V latencies (ms) published previously*

	I	III	V
Rosenblum (1982) [12]	1.6	3.7	5.8
Samra (1984) [13]	1.7	3.9	5.8
Picton (1974) [14]	1.5	3.8	5.8
Thornton (1983) [4]	1.6	3.7	5.8

Statistics

Data are presented as mean (SEM).

The Wilkoxon matched-pairs test was used to compare T1, T2 and T3 with basal data. $P < 0.05$ was taken as significant.

RESULTS

The basal values for waves I, III, V latency in our subjects were similar to published data (table I).

The measured latencies and amplitudes for all subjects are shown in table II.

TABLE II. *Latencies, amplitudes and conduction times (mean (SEM)) associated with different infusion rates of propofol* *P < 0.05, **P < 0.01

		Basal	T1 (7 mg kg^{-1} h^{-1})	T2 (5 mg kg^{-1} h^{-1})	T3 (3 mg kg^{-1} h^{-1})
Latency (ms)	I	1.65 (0.03)	1.70 (0.05)*	1.70 (0.04)*	1.70 (0.04)*
	III	3.85 (0.06)	3.93 (0.06)**	3.94 (0.06)**	3.93 (0.05)*
	V	5.73 (0.06)	5.85 (0.07)*	5.83 (0.05)*	5.89 (0.07)*
	Pa	27.8 (0.94)			
	Nb	30.6 (1.45)			
Conduction time (ms)	I–III	2.22 (0.03)	2.24 (0.06)	2.23 (0.04)	2.24 (0.07)
	I–V	4.08 (0.05)	4.15 (0.07)	4.14 (0.04)	4.19 (0.06)
	III–V	1.85 (0.06)	1.91 (0.05)	1.90 (0.04)	1.94 (0.02)
Amplitude (μV)	I	0.33 (0.07)	0.30 (0.07)	0.30 (0.06)	0.32 (0.06)
	III	0.28 (0.06)	0.25 (0.06)	0.26 (0.06)	0.26 (0.06)
	V	0.38 (0.04)	0.36 (0.03)	0.35 (0.04)	0.36 (0.04)
	Pa–Nb	1.00 (0.2)			
Blood concn of propofol (μg ml^{-1})			2.44 (0.16)	2.08 (0.11)	1.60 (0.14)

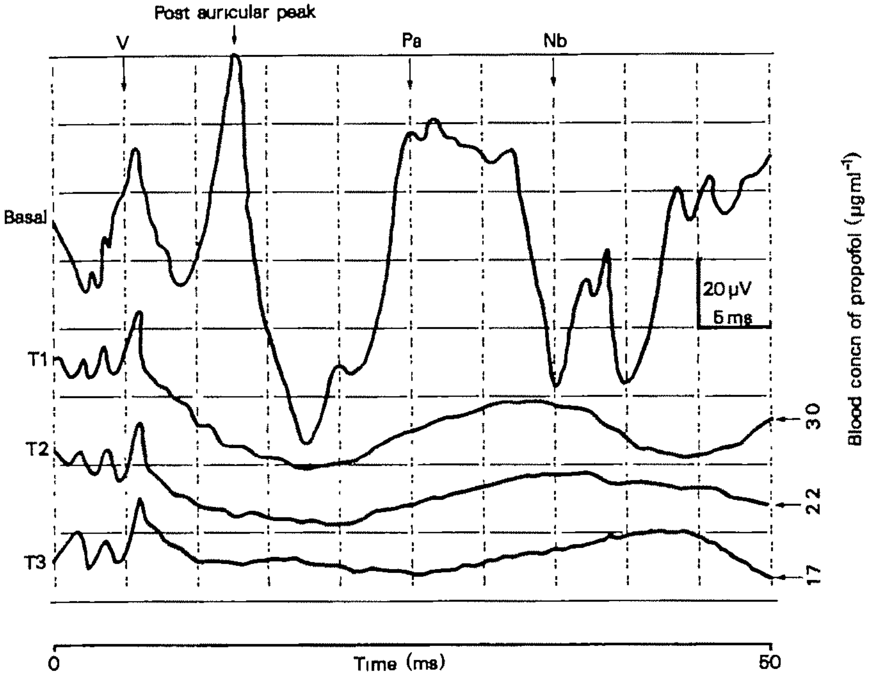

FIG. 1 BAEP for one subject before anaesthesia and at different concentrations of propofol. Arrows indicate the position of waves V, Pa and Nb. Filters. 5–1000 Hz; count: 512; stimulus rate. 5 Hz; duration: 0.1 ms.

Brainstem waves were identified easily in all subjects. Peak latencies I, III, V recorded at T1, T2 and T3 increased significantly compared with control values, but did not exceed 5%. Amplitudes also decreased, but changes were not significant. Numerical values for conduction times (I–III, III–V, I–V) are shown in table II.

Basal early cortical waves were analysed in six subjects, but they were affected by the propofol infusion (fig. 1). For this reason, amplitude and latency measurements were not obtained for T1, T2 and T3 (table II).

Body temperature remained within 0.5 °C of the preinduction value in all patients. During the study end-tidal carbon dioxide concentration remained constant at 4.8 (0.2) kPa.

The infusion of propofol caused a decrease in systolic, mean and diastolic arterial pressure (table III), but only the changes in systolic arterial pressure were significant (T2). Arterial pressures remained within 17% of control values.

Blood concentrations of propofol (table II) were similar to data obtained in previous studies during maintenance of general anaesthesia (1–3 µg ml⁻¹).

DISCUSSION

Isoflurane [15], etomidate [16], thiopentone and propofol [17] increase cortical peak latency N20 during somatosensory evoked potential recording (SEP), but do not increase cervical peak latency

TABLE III. *Haemodynamic data (mean (SEM)). SAP = Systolic arterial pressure; MAP = mean arterial pressure, DAP = diastolic arterial pressure* $**P < 0.01$, *rest not significantly different, compared with basal value*

	Basal	T1	T2	T3
SAP (mm Hg)	132 (5.9)	123 (6.6)	113 (5.4)**	114.3 (5.6)
MAP (mm Hg)	86 (3.4)	82.5 (4.4)	77.6 (2.8)	79.5 (3.7)
DAP (mm Hg)	66 (2.7)	64.6 (3.6)	61.9 (3.1)	61.6 (3.4)

N13. Central conduction time also is altered by these drugs. The volatile agents halothane, enflurane and isoflurane alter BAEP [18], but BAEP is more resistant to i.v. anaesthetic agents. Only large doses of thiopentone prolong BAEP pic waves [19]. As described previously [4], we found that, whilst the latencies of brainstem waves were affected, we did not observe concomitant changes in peak amplitude which are normally associated with latency changes throughout the nervous system. This suggests that neural events were delayed, probably at the sites of synaptic transmission [20]. *In vitro* studies have shown that propofol alters mitochondrial metabolism, reduces mitochondrial oxygen consumption, and reduces ionic transfer [21]. This probably contributes to the neuronal effect of propofol.

Thornton and colleagues [6] have speculated that BAEP changes produced by some anaesthetics agents may correlate with their cardiorespiratory side effects. Our data are consistent with this hypothesis, but at present it is not possible to state at what level sensory transmission is first affected because we found that propofol decreased both brainstem and early waves. Nevertheless, the changes in BAEP indicate a definite alteration in brainstem function. This is consistent with clinical signs of brainstem dysfunction such as ataxia and tremor that have been described previously in acute intoxication with oral propofol [22].

For the six patients in whom the early component was analysed, myogenic, Pa and Nb peaks were not identified clearly during the infusion of propofol. Previous studies showed that Pa was resistant to natural sleep [23], secobarbitone and diazepam sedation [24, 25], and that Pa, Nb were resistant to vecuronium and anaesthesia induced by fentanyl [26].

Previous studies have shown that high anaesthetic concentrations (end-tidal concentrations up to 1.3 % for halothane [5], up to 1.22 % for enflurane [4] and plasma concentrations up to 0.66 ng ml^{-1} for etomidate [6]) altered middle latency auditory evoked responses. The same changes were found to occur in our study with comparatively low plasma propofol concentrations (1.7 μg ml^{-1}) (fig. 1). The diverse structure of these agents suggests a relatively nonspecific mechanism of action. The high lipid solubility of propofol may explain its ability to alter BAEP in low concentrations.

Changes in temperature, arterial pressure and blood-gas tensions are known to affect BAEP. However, Jones [27] demonstrated that temperature changes of less than 0.5 °C, similar to those obtained here, did not produce significant changes in BAEP.

A decrease in systolic arterial pressure (SAP) of more than 20 % [28] has been reported to affect sensory evoked potentials (SEP). In our study the change in SAP induced by propofol was less than 14 % (28 mm Hg), and SAP always exceeded 100 mm Hg. These haemodynamic changes induced by propofol agree with those observed by other authors [29]. Cerebral perfusion was probably affected minimally during our study, as Coates and colleagues [30] observed only a 6 % reduction in cardiac index with propofol, despite a marked reduction in SAP. Lam [2] and Samra [12] observed, during SEP recording, a reduction in MAP of 11 %. This change was similar to that observed by McLeod [31] and was associated with similar minimal effects on SEP, as noted elsewhere [32].

To minimize drug effects on BAEP, we used hydroxyzine and a benzodiazepine for premedication as Stockard and colleagues [33] showed that these drugs have no effect on BAEP recording. There is also no evidence that neuromuscular blocking agents alter BAEP [26].

We conclude that propofol anaesthesia alters BAEP and that a prolongation of BAEP by more than 5 % during neurosurgery would suggest the presence of factors in addition to anaesthesia, such as operative manipulation, retraction, hypocapnia or arterial hypotension.

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EFFECT OF KETANSERIN ON SODIUM NITROPRUSSIDE REQUIREMENTS, ARTERIAL PRESSURE CONTROL AND HEART RATE FOLLOWING CORONARY ARTERY BYPASS SURGERY

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SUMMARY

In a double-blind, placebo controlled study ketanserin, a serotonin S_2 antagonist, was administered to hypertensive patients who had undergone coronary artery bypass surgery. Patients were allocated randomly to receive placebo or ketanserin at an infusion rate of 0.05, 1 or 2 mg kg^{-1} h^{-1}. Sodium nitroprusside was used as escape medication. Ketanserin reduced the nitroprusside requirements and improved the quality of arterial pressure control in all groups, and this was significant in the low- and high-dose groups. There was a significant decrease in heart rate in the low- and high-dose groups compared with placebo, and no effect in patients who received the medium dose of ketanserin. Ketanserin may be a useful treatment for hypertension following coronary artery surgery as it reduced arterial pressure without reflex tachycardia

Between 30 and 60% of patients develop early hypertension following cardiac bypass surgery and require the administration of short-acting vasodilator agents [1, 2]. This early hypertension develops within the first 4–6 h after cardiopulmonary bypass, and is associated with many factors, including patient arousal, pain and tracheal suction. The presence of increased concentrations of circulating catecholamines, serotonin and activation of the renin–angiotensin system also may contribute [3, 4]. Close control of arterial pressure is necessary to reduce the incidence of bleeding from suture lines and protect the myocardium from ischaemia [1, 3]. Sodium nitroprusside (SNP) is one of the most commonly used agents; however, it can cause reflex tachycardia and, by reducing diastole, can lead to a decrease in coronary blood flow, especially to the endocardium.

Ketanserin is a serotonin S_2 receptor antagonist with weak alpha-1 blocking properties. It has been shown to reduce systemic arterial pressure by decreasing peripheral vascular resistance without causing reflex tachycardia [5]. It causes peripheral arteriolar dilatation, thereby decreasing left ventricular afterload, and may reduce right atrial pressure by venodilatation or indirectly by an improvement in left ventricular function [6]. Ketanserin has been shown also to prolong the duration of the cardiac action potential and has properties similar to Class III antiarrhythmic drugs [7]. These features should make it a useful vasodilator after cardiac surgery, reducing myocardial work and oxygen consumption. Several studies have shown ketanserin to be effective in reducing arterial pressure [5–8], but a wide range of infusion rates has been used and the optimum dose for the acutely hypertensive patient has not been determined.

A double-blind, placebo-controlled study was undertaken to determine the efficacy of ketanserin in patients who had undergone elective coronary artery bypass surgery and who required antihypertensive therapy. SNP was used as escape medication and was delivered by a computer-controlled closed-loop system which has been shown in previous studies to provide better control of arterial pressure than that provided with manual alteration of vasodilators by nursing staff [9, 10].

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PATIENTS AND METHODS

We studied patients undergoing elective coronary artery bypass grafting (CABG) following their informed consent. Patients were not included if they were aged less than 30 or more than 70 yr, weighed less than 45 kg or more than 100 kg, lost more than 1 litre of blood after operation or had severe hepatic, renal or respiratory disease.

All patients received an opioid–midazolam based anaesthetic and all underwent elective ventilation to normocapnia in the cardiac intensive care unit after operation. Monitoring consisted of continuous measurement of ECG, direct arterial pressure and core temperature, with intermittent recordings of central venous pressure and urine output. Arterial blood-gas values, haematocrit and potassium concentrations were measured at the discretion of the cardiac surgeons and also at the start and end of the study.

Patients who had given informed consent and who required vasodilator therapy for post-surgical hypertension were entered into the study and connected to a closed-loop arterial pressure controller which consisted of an Atari 1040 ST microcomputer interfaced to a computer-controlled IMED 929 infusion pump. Sodium nitroprusside, in a dilution of 100 mg in 5% dextrose 250 ml was used as escape medication in all patients initially, but this concentration was doubled if the SNP requirements were high and there was concern over the volume of fluid administered. The cardiac surgeons prescribed the desired target systolic arterial pressure for each patient.

Ketanserin may prolong the Q–T interval [11] and there have been reports of ventricular arrhythmias [12]. As hypokalaemia also prolongs QT_c (corrected Q–T interval) and is a risk factor for arrhythmia, patients with a serum potassium concentration of less than 3.5 mmol litre^{-1} were not included in the study until administration of potassium had increased the serum concentration to a value greater than 3.5 mmol litre^{-1}. The ECG for each patient was examined before operation and during the infusion of test drug to determine the effect of ketanserin on the Q–T interval.

Patients were allocated randomly to one of four groups:

(a) Group P received placebo: a bolus dose of 10 ml followed by an i.v. infusion.

Each patient allocated to receive ketanserin was given a loading i.v. dose of 10 mg in saline 10 ml followed by an infusion:

(b) Group L (low dose) received 0.05 mg kg^{-1} h^{-1}

(c) Group M (medium dose) received 0.1 mg kg^{-1} h^{-1}

(d) Group H (high dose) received 0.2 mg kg^{-1} h^{-1}

The infusion was given for a maximum of 8 h or until the SNP requirements had been zero for 30 min.

The arterial pressure, heart rate, quality of arterial pressure control as assessed by variation from the prescribed target pressure, SNP infusion rate and total volume of SNP infused were recorded for each patient on to computer disk every 1 min during the administration of the trial drug and for 1 h after the infusion had been discontinued. The patients received midazolam and morphine at the discretion of the nursing or medical staff. No addition vasodilator or antihypertensive therapy was permitted.

Demographic data were analysed using Student's *t* test. Non-parametric data were analysed by a two-tailed Mann–Whitney *U* test or Chi-square test.

RESULTS

Forty-four patients were entered into the study; three were excluded from subsequent analysis: two because of errors in data collection and one after receiving propranolol for persistent tachycardia. There were 10 patients in groups P, L and M, and 11 patients in group H.

There was no significant difference between the group for age, weight or sex (table I).

There was a small (0.6 °C) but statistically

TABLE I. *Comparison of age, weight, sex and initial temperature (mean (SD)).* *P < *0.05*

	Group P	Group L	Group M	Group H
Age (yr)	54.4 (7.7)	53.9 (8.9)	56.7 (6.5)	53.1 (9.1)
Sex (M.F)	7:3	9:1	9:1	10:1
Weight (kg)	77.5 (6.5)	79.6 (9.9)	76.3 (4.7)	77.7 (11)
Temperature at start (°C)	35.1 (1.5)	35.5 (0.5)*	35.2 (1.1)	34.7 (0.6)

TABLE II. *Median (range) duration of test infusions.* *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

	Group P	Group L	Group M	Group H
Duration (h)	7.2 (1.7–8.0)	3.0 (0.5–8.0)*	3.0 (0.5–7.3)*	2.1 (0.6–7.8)***

TABLE III *SNP requirements (median (range)).* *$P < 0.05$, **$P < 0.01$; ***$P < 0.001$

Volume of SNP infused (ml)	Group P	Group L	Group M	Group H
First 30 min after bolus of trial drug	12 (2–44)	3 (0–10)**	8 (0–36)	3 (0–15)***
While trial drug infused	111 (9–780)	17 (0–333)*	54 (0–204)	11 (1–168)***
Per hour of study	22 (5–95)	6 (0–42)*	11 (0–33)	7 (1–22)***
First 1 h after infusion	5 (0–98)	4 (0–43)	1 (0–5)*	0 (0–20)*

significant difference between groups L and H for core temperature at the start of the study ($P < 0.05$). There were no significant differences between the groups for target pressure assigned by the surgeon or for blood loss during the study.

There were no significant differences between the groups for the numbers of patients treated before operation with beta-blockers, or for the numbers treated with the longer acting drug, atenolol.

Duration of test infusions

The test infusions were discontinued after 8 h or when the SNP requirements had been zero for 30 min. The durations of infusions of the trial drug were analysed for each patient (table II). The median times during which the trial drugs were infused were significantly less for all patients receiving ketanserin compared with those receiving placebo.

Nitroprusside requirements

The sodium nitroprusside requirements at various periods for the four groups are shown in table III. At 30 min from the start of the test infusion, and for the entire duration of the study, patients receiving ketanserin required less SNP than those who received placebo, although the difference was not significant for those in group M. As the durations of test infusions were significantly different, the mean hourly requirements of SNP during the infusions were analysed for each group. The patients who received ketanserin required less SNP per hour during ketanserin infusion, and this was significant in group L ($P < 0.05$) and group H ($P < 0.001$). When the infusions had been discontinued, the SNP requirements for the next 1 h were such that those patients who received medium and high doses of ketanserin needed less SNP than group L ($P < 0.05$, $P < 0.05$, respectively) although the differences were not significant compared with group P.

The median SNP requirements from the time of arrival in the intensive care unit until entry into the study (administration of trial drug) were significantly different (table IV): group P required less SNP than groups M and H ($P < 0.05$), and group L required less than group M ($P < 0.01$) and group H ($P < 0.05$).

Quality of arterial pressure control

The quality of control arterial pressure was assessed as a percentage of the time spent outside the target pressure ±10 mm Hg (table V). There was no significant difference between the groups for percentage time spent at pressures more than 10 mm Hg below the target, or for pressure

TABLE IV *Median (range) volume (ml) of SNP required in the 10 min before bolus dose given* *$P < 0.05$, **$P < 0.01$ *compared with placebo*; †$P < 0.05$ *compared with low-dose group*

	Group P	Group L	Group M	Group H
Volume (ml)	0.6 (0.3–4.3)	1.1 (0.4–2.1)	2.7 (0.9–9–10)**†	3.5 (0.5–7.2)*†

TABLE V. *Quality of arterial pressure control. % time spent at pressures greater than 10 mm Hg above target pressure (median (range)). Compared with group P: *P < 0.05; **P < 0.01; ***P < 0.001*

	Time at target + 10 mm Hg (%)			
	Group P	Group L	Group M	Group H
0–1 h	21 (3–37)	3 (0–45)*	12 (2–27)	7 (0–18)***
0–2 h	19 (4–33)	4 (0–41)*	10 (3–21)	4 (0–17)**

greater than target at times over 2 h. These results show that better quality of control of arterial pressure was achieved in all groups, although this did not reach significance in the medium dose group.

Ketanserin and heart rate

Previous studies have shown that ketanserin tends to reduce or have minimal effect on heart rate, whereas SNP tends to produce tachycardia [5, 13, 14]. Mean heart rate for each patient was analysed for 10 min before ketanserin was administered, and for the 10 min after the bolus dose was given. There was a significant increase in heart rate 10 min after the bolus dose of placebo had been given compared with the heart rate before administration ($P < 0.05$), but a significant decrease in heart rate in the low- and high-dose groups compared with the heart rate before ketanserin had been given ($P < 0.05$). These results (table VI) confirm that ketanserin does not cause tachycardia.

ECG recordings of all the patients were obtained before operation and also during the study to determine the effect of ketanserin on the corrected Q–T interval ($QT_{(cor)}$). No significant differences were found between the groups for $QT_{(cor)}$ before or after the infusion of ketanserin, and there was no significant change in $QT_{(cor)}$ within each group.

DISCUSSION

We have shown that ketanserin controlled hypertension following coronary artery bypass surgery; this is in agreement with previous findings [15, 16].

At the beginning of the study, the bolus dose of trial drug was given slowly but undiluted and this produced a marked, rapid decrease in systolic arterial pressure in two patients. Both these patients were found subsequently to have received the active drug and they also had relatively low central venous pressures. The arterial pressure returned to acceptable values with rapid i.v. infusion of fluid. All subsequent bolus doses were diluted thereafter and injected over a period of 10 min, without adverse effect on arterial pressure.

TABLE VI *Effect of ketanserin on heart rate (beat min^{-1}) 10 min before bolus dose and 10 min after bolus (mean (SD)). *P < 0.05*

	Group P	Group L	Group M	Group H
Before bolus	84 (16)	86 (10)	87 (12)	100 (24)
After bolus	89 (16)*	83 (8)*	87 (11)	96 (24)*

The effects of ketanserin and SNP were found to be additive and ketanserin infusion reduced the requirement for SNP, resulting in a reduced duration and volume of SNP infusion.

SNP requirements from the time of admission into the intensive care unit until the study commenced showed that patients in the medium- and high-dose groups required significantly more SNP than patients in either the placebo or the low-dose group. Analysis of SNP requirements during the period before the study suggested that the arterial pressure of patients in the medium- and high-dose groups was significantly more difficult to control. While the high dose of ketanserin appeared to be adequate in overcoming this difficulty, the medium dose was not.

The quality of arterial pressure control for patients who received ketanserin was better compared with those in the placebo group. There was no significant differences between the treated groups and placebo for the percentage time spent below the target pressure, indicating that although ketanserin reduced arterial pressure, it did not do so excessively.

Our data on the effect of ketanserin on heart rate support other studies [15], in that patients who received ketanserin did not exhibit reflex tachycardia. Analysis of the individual ECG records of each patient showed that in this study, in contrast with the small prolongation of $QT_{(cor)}$ reported previously after oral use [11], ketanserin had no effect on the corrected Q–T interval.

Several patients developed ECG abnormalities during treatment (two in the placebo group, two in the ketanserin low-dose group and two in the high-dose group); these were considered to be caused by patient arousal or, in one patient (ketanserin high dose), by a low concentration of potassium.

One patient, who had been allocated to receive the high dose of ketanserin, had short periods of ventricular bigemini and trigemini, alternating with intermittent bradycardia and 1st degree heart block for a few seconds. The arterial pressure remained stable throughout. However, the possibility of this response being related to the trial drug could not be excluded.

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EFFECTS OF PROPOFOL ON PULMONARY AND SYSTEMIC ARTERIAL PRESSURE–FLOW RELATIONSHIPS IN HYPEROXIC AND HYPOXIC DOGS

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SUMMARY

We have investigated the effects of a continuous infusion (18 mg kg^{-1} h^{-1}) of the aqueous emulsion formulation of propofol on mean pulmonary arterial (PAP)/cardiac output ($\dot{Q}$) and mean systemic arterial pressure (SAP)/$\dot{Q}$ relationships in 15 intact pentobarbitone-anaesthetized dogs subjected to hyperoxia ($F_{I_{O_2}}$ 0.4) and hypoxia ($F_{I_{O_2}}$ 0.1). Five-point PAP/$\dot{Q}$ and SAP/$\dot{Q}$ plots were obtained by opening an arterio–venous femoral fistula or by stepwise inflations of an inferior vena cava balloon. Over the range of $\dot{Q}$ studied (2–5 litre min^{-1}), hypoxia increased PAP in eight dogs ("responders") and did not affect PAP in seven others ("non-responders"). Hypoxic pulmonary vasoconstriction (HPV) was restored in non-responders by the administration of acetylsalicylic acid (ASA) 1 g i.v. Hypoxia did not affect SAP over the range of $\dot{Q}$ studied in the responders or in the non-responders treated with ASA. Propofol had no effect on hyperoxic or on hypoxic PAP at all values of $\dot{Q}$ either in responders or in non-responders with HPV restored by ASA. Propofol did not change $\dot{Q}$ at uncontrolled flow, but decreased SAP at the lowest $\dot{Q}$ (2 and 3 litre min^{-1}) during hyperoxia and at all values of $\dot{Q}$ during hypoxia The systemic vascular effects were the same in animals of both groups, treated with ASA or not. We conclude that propofol does not influence pulmonary vascular tone and does not inhibit HPV, but reduces systemic vascular tone when venous return or oxygenation is decreased. The haemodynamic response to propofol was not affected by cyclo-oxygenase inhibition.

In doses required to produce surgical anaesthesia, propofol has been reported to induce variable decreases in cardiac output and systemic arterial pressure, and at least part of these systemic hypotensive effects has been attributed to a decrease in systemic vascular tone [1–7]. The effects of propofol on pulmonary vascular tone have not yet been investigated.

Because of the characteristics of the pulmonary and systemic vascular pressure–cardiac output relationships, single pressure:flow ratio calculations such as pulmonary vascular resistance (PVR) (mean pulmonary arterial pressure (PAP) minus pulmonary capillary wedge pressure (PCWP) (assumed equal to left atrial pressure) divided by cardiac output ($\dot{Q}$)) and systemic vascular resistance (SVR) (mean systemic arterial pressure (SAP) minus right atrial pressure (RAP) divided by $\dot{Q}$) are unreliable in evaluating changes in pulmonary and systemic vascular tone [8]. When resistance is defined as arterial minus venous pressure divided by flow, one assumes that this pressure–flow relationship is linear and passes through the origin. PAP/$\dot{Q}$ relationships are linear over a physiological range of flows, but the extrapolated pressure intercepts of (PAP − PCWP)/$\dot{Q}$ plots are positive in most clinical and experimental circumstances [9]. SAP/$\dot{Q}$ relationships are non-linear and extrapolated pressure intercepts of (SAP − RAP)/$\dot{Q}$ plots also are positive [8]. It is thus necessary to obtain SAP and PAP measurements over a wide range of flows in order to interpret the effects of a drug or a physiological intervention on the pulmonary and the systemic systems [8, 9]. We have recently reported this approach to investigate the pulmonary haemodynamic effects of inhaled anaesthetics in intact dogs [10, 11]. In the present

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study, PAP/$\dot{Q}$ and SAP/$\dot{Q}$ plots were constructed in intact hyperoxic and hypoxic dogs before and after the administration of propofol in clinically relevant doses.

MATERIALS AND METHODS

Fifteen mongrel dogs (22–33 kg, mean 25) were anaesthetized with pentobarbitone 30 mg kg^{-1} i.v., paralysed with pancuronium bromide 0.2 mg kg^{-1} i.v., placed in the supine position and the lungs ventilated mechanically (12 b.p.m.) (Elema 900 B Servo-ventilator, Siemens, Solna, Sweden) via a cuffed tracheal tube; the inspired gas was 40 % oxygen in nitrogen and the tidal volume 15–20 ml kg^{-1} adjusted to maintain arterial $P\text{CO}_2$ between 4.0 and 4.7 kPa. Positive end-expiratory pressure was not used. Administration of pentobarbitone 2 mg kg^{-1} and pancuronium 0.2 mg kg^{-1} i.v. was repeated hourly to maintain anaesthesia and prevent spontaneous ventilatory efforts. Throughout the experiment, normal saline was infused at a rate of 4 ml kg^{-1} h^{-1} via the left external jugular vein. Metabolic acidosis was corrected by a slow infusion of sodium bicarbonate. Temperature was maintained at 37–38 °C by use of an electric heating pad.

A thermistor-tipped Swan–Ganz catheter (model 93A-131-7F, Edwards Laboratories, Santa Ana, Ca) was inserted via the right external jugular vein and positioned by means of pressure monitoring in a branch of the pulmonary artery for measurements of pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP) and mixed venous blood sampling. A polyethylene catheter was placed in the abdominal aorta via the right femoral artery for measurement of SAP and arterial blood sampling. A balloon catheter (Pericor 45 Datascope, Paramus, NJ) was advanced into the inferior vena cava through a right femoral venotomy. Inflation of this balloon produced a controlled decrease in cardiac output by reduction of venous return. A large-bore polyethylene cannula was inserted into the left femoral artery and vein to act as an arterio–venous fistula. Increasing venous return by opening this fistula resulted in an increase in cardiac output by an average of 0.4 litre min^{-1}. Thrombus formation along the catheters was prevented by administration of heparin 150 u. kg^{-1} i.v. just before their insertion and 50 u. kg^{-1} i.v. repeated every 2 h thereafter.

Pulmonary and systemic artery pressures were measured using Bentley transducers and the Hemodynamic and Respiratory Computer System (H.E.R.E.S., Ateliers de Construction Electrique, Charleroi, Belgium) and recorded on a four-channel Gould recorder (model 2400 S, Gould Inc., Instruments Division, Cleveland, Oh). The zero reference was the mid-chest level and vascular pressures were measured at end-expiration. Heart rate (HR) was obtained from a continuously monitored electrocardiograph lead. Cardiac output was measured by thermodilution using injection of 0.9 % sodium chloride 10 ml at 0 °C, a computer (9520-A Edwards Laboratories) and an automated pneumatic pump synchronized electronically with the ventilatory cycle; the mean of three determinations was taken. Arterial and mixed venous pH, $P\text{CO}_2$ and $P\text{O}_2$ were measured immediately after the samples were drawn by an automated analyser (ABL2, Radiometer, Copenhagen, Denmark) and corrected for temperature.

In all the dogs, after steady-state conditions were obtained for 20 min at $F\text{I}_{\text{O}_2}$ 0.4 (stable SAP, PAP and HR), the first five-point PAP/$\dot{Q}$ and SAP/$\dot{Q}$ plots were generated from haemodynamic determinations at base line (one point), after opening the arterio–venous fistula (one point) and after stepwise incremental inflations of the inferior vena cava balloon with the fistula occluded (three points). The same was repeated after 6 min with $F\text{I}_{\text{O}_2}$ 0.1. One five-point plot was generated in 25–30 min.

When hypoxia induced an increase in PAP of more than 3 mm Hg at an identical $\dot{Q}$ of 3 litre min^{-1}, obtained by inflation of the inferior vena cava balloon during the construction of the pressure/$\dot{Q}$ curves ("responders", eight dogs), propofol 18 mg kg^{-1} h^{-1} was given as a continuous infusion (calibrated pump, Braun Melsungen AG, Melsungen, F.R.G.). This dose is at the upper limit of the recommended range to maintain general anaesthesia in patients [12, 13]. Pentobarbitone was omitted after the administration of propofol was commenced. A sequence of pressure/$\dot{Q}$ plots at $F\text{I}_{\text{O}_2}$ 0.4 and 0.1 successively was repeated at the 20th min of the propofol infusion.

When hypoxia did not change PAP by more than 3 mm Hg at identical $\dot{Q}$ of 3 litre min^{-1} ("non-responders", seven dogs) a 1-g bolus of acetylsalicylic acid (ASA) was given to enhance or restore the hypoxic pulmonary pressor response as reported previously [10, 11]. After 45 min, a second sequence of pressure/$\dot{Q}$ plots at $F\text{I}_{\text{O}_2}$ 0.4

and 0.1 successively was generated, followed by a third sequence of plots at FI_{O_2} 0.4 and 0.1 at the 20th min of an infusion of propofol 18 mg kg^{-1} h^{-1}.

Arterial and mixed venous blood-gas tensions were measured at the highest and at the lowest $\dot{Q}$ of each pressure/$\dot{Q}$ plot. Measurements of PCWP and RAP were made at each point of the plots.

In three responders and in three non-responders, plasma concentrations of propofol were measured by high pressure liquid chromatography [14] every 20 min during the construction of the hyperoxic and hypoxic pressure/$\dot{Q}$ plots (respectively 20, 40, 60, 80 and 100 min after starting the continuous infusion of propofol).

The shape of the PAP/$\dot{Q}$ and the SAP/$\dot{Q}$ relationships was examined using a stepwise polynomial regression. Increasingly higher order terms were added one at a time to a least square polynomial fitting and the regression coefficient for the added term was tested by an analysis of variance at the 0.05 level of significance. If the regression coefficient was found not significant, the polynomial regression of lower order was retained as the best fit for the pressure/$\dot{Q}$ relationship. This relationship was examined separately for each dog in each experimental condition. To obtain composite plots, PAP and SAP interpolated from the regression analysis from individual dogs were averaged at 1-litre min^{-1} intervals of $\dot{Q}$ from 2 to 5 litre min^{-1} and presented as mean (SEM). The blood-gas and haemodynamic data at the greatest and at the smallest value of $\dot{Q}$ were analysed by a repeated-measures analysis of variance. When the F ratio of the analysis of variance achieved $P < 0.05$, Student's modified t tests were used to compare two specific situations. Repeated measures analyses of variance were performed also to analyse the effects of hypoxia and drugs on pressure/$\dot{Q}$ plots, and when the F ratio reached $P < 0.05$, Student's modified t tests were performed to compare PAP and SAP at each level of flow [15].

RESULTS

Variation in cardiac output

Cardiac output was varied between 2 and 5 litre min^{-1} (tables I, II). Over this range of flows, the majority of the PAP/$\dot{Q}$ and SAP/$\dot{Q}$ relationships were found to be linear. The best fit for PAP/$\dot{Q}$ plots was a first-order polynomial in six or seven of eight dogs or six to seven of seven dogs in all the experimental situations, the remainder being

TABLE I *Haemodynamic data and blood-gas tensions in eight dogs given propofol during hyperoxia and during hypoxia (mean (SEM)) H = highest $\dot{Q}$; L = lowest $\dot{Q}$, pHa = arterial pH*; Pa_{O_2} *= arterial* PO_2, Pa_{CO_2} *= arterial* PCO_2; $P\bar{v}_{O_2}$ *= mixed venous* PO_2 *(for other abbreviations see text) Significant changes* ($P < 0.05$): ** compared with hyperoxia baseline, † compared with hypoxia baseline*

		Hyperoxia		Hypoxia	
	$\dot{Q}$	Baseline	Propofol	Baseline	Propofol
pHa	H	7.35 (0.02)	7.33 (0.01)	7.39 (0.01)	7.38 (0.01)
	L	7.36 (0.01)	7.33 (0.01)	7.38 (0.02)	7.36 (0.01)
Pa_{O_2} (kPa)	H	29.2 (1.2)	27.4 (1.5)*	5.3 (0.1)*	4.8 (0.3)†
	L	29.2 (1.1)	27.6 (1.3)*	5.7 (0.1)*	4.9 (0.1)†
Pa_{CO_2} (kPa)	H	4.5 (0.1)	4.5 (0.1)	4.1 (0.1)	4.3 (0.1)
	L	4.1 (0.1)	4.4 (0.1)	3.1 (0.1)*	3.9 (0.1)
$P\bar{v}_{O_2}$ (kPa)	H	7.9 (0.3)	7.7 (0.3)	4.4 (0.1)*	3.7 (0.1)†
	L	5.3 (0.1)	5.5 (0.3)	3.3 (0.1)*	2.9 (0.1)†
$\dot{Q}$ (litre min^{-1})	H	4.5 (0.5)	4.1 (0.3)	5.1 (0.5)*	5.2 (0.5)
	L	1.6 (0.2)	1.9 (0.2)	1.6 (0.2)	2.1 (0.1)
HR (beat min^{-1})	H	148 (5)	119 (10)*	165 (7)*	138 (9)†
	L	154 (8)	120 (6)*	153 (8)	132 (7)†
SAP (mm Hg)	H	109 (8)	109 (5)	140 (7)*	102 (6)†
	L	87 (12)	61 (6)*	88 (11)	53 (4)†
PAP (mm Hg)	H	15 (1)	15 (1)	26 (1)*	28 (2)
	L	9 (1)	9 (1)	14 (1)*	16 (1)
PCWP (mm Hg)	H	5 (1)	6 (1)	6 (1)	5 (1)
	L	3 (1)	2 (1)	2 (1)	2 (1)
RAP (mm Hg)	H	3 (1)	4 (1)	4 (1)	4 (1)
	L	2 (1)	2 (1)	1 (1)	1 (1)

TABLE II. *Effects of acetylsalicylic acid (ASA) followed by propofol on haemodynamic data and blood-gas values in seven dogs during hyperoxia and hypoxia (mean (SEM)) Significant changes ($P < 0.05$): * compared with hyperoxia baseline; † compared with hyperoxia ASA; ‡ compared with hypoxia baseline, § compared with hypoxia ASA*

		Hyperoxia			Hypoxia		
	$\dot{Q}$	Baseline	ASA	Propofol	Baseline	ASA	Propofol
pHa	H	7.37 (0.01)	7.34 (0.02)	7.32 (0.02)†	7.39 (0.01)	7.36 (0.02)	7.35 (0.02)§
	L	7.38 (0.01)	7.34 (0.02)*	7.34 (0.02)†	7.39 (0.02)	7.36 (0.03)	7.34 (0.03)
Pa_{O_2} (kPa)	H	27.7 (1.3)	26.5 (1.3)	26.6 (1.6)	5.6 (0.1)*	5.5 (0.4)	4.7 (0.3)§
	L	26.5 (1.7)	26.1 (1.5)	25.2 (2.0)	5.7 (0.3)*	5.3 (0.3)	4.9 (0.3)
Pa_{CO_2} (kPa)	H	4.5 (0.1)	4.5 (0.1)	4.7 (0.3)	4.1 (0.1)*	4.4 (0.3)	4.7 (0.3)
	L	4.0 (0.3)	4.3 (0.3)	4.4 (0.3)	3.7 (0.1)*	4.0 (0.3)	4.4 (0.3)
$P\bar{v}_{O_2}$ (kPa)	H	7.7 (0.4)	7.2 (0.4)	7.6 (0.3)	4.3 (0.1)*	4.5 (0.3)	3.6 (0.3)§
	L	5.2 (0.1)	5.6 (0.3)	5.5 (0.1)	3.5 (0.1)*	3.7 (0.3)	2.9 (0.1)
$\dot{Q}$ (litre min^{-1})	H	4.5 (0.4)	4.5 (0.5)	4.6 (0.5)	5.4 (0.3)*	6.2 (0.5)	5.9 (0.7)
	L	1.7 (0.1)	1.9 (0.2)	2.1 (0.1)	2.0 (0.1)	2.4 (0.3)	2.5 (0.3)
HR (beat min^{-1})	H	144 (7)	136 (8)	122 (8)†	150 (9)	156 (8)	142 (11)
	L	174 (14)	166 (7)	131 (11)†	147 (8)	153 (6)	134 (14)
SAP (mm Hg)	H	113 (6)	120 (6)	109 (8)	139 (7)	147 (10)	113 (14)§
	L	89 (9)	88 (9)	68 (7)†	72 (9)	96 (12)‡	69 (8)§
PAP (mm Hg)	H	14 (1)	15 (1)	16 (1)	18 (1)*	25 (2)‡	25 (2)
	L	8 (1)	9 (1)	9 (1)	10 (1)*	14 (1)‡	15 (2)
PCWP (mm Hg)	H	6 (1)	6 (1)	7 (1)	6 (1)	7 (1)	7 (1)
	L	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)	4 (1)
RAP (mm Hg)	H	4 (1)	4 (1)	4 (1)	4 (1)	4 (1)	5 (1)
	L	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)	3 (1)

TABLE III *Best fit for pulmonary arterial pressure–cardiac output relationships in hyperoxic and hypoxic dogs before and after administration of propofol*

	Polynomial order			
	Zero	First	Second	Third
Responders ($n = 8$)				
$F\text{I}_{O_2}$ 0.4	1	6	1	0
$F\text{I}_{O_2}$ 0.1	1	6	1	0
$F\text{I}_{O_2}$ 0.4 + propofol	1	6	1	0
$F\text{I}_{O_2}$ 0.1 + propofol	1	7	0	0
Non-responders ($n = 7$)				
$F\text{I}_{O_2}$ 0.4	0	6	1	0
$F\text{I}_{O_2}$ 0.1	0	6	1	0
$F\text{I}_{O_2}$ 0.4 + ASA	0	6	1	0
$F\text{I}_{O_2}$ 0.1 + ASA	0	6	1	0
$F\text{I}_{O_2}$ 0.4 + ASA + propofol	0	6	1	0
$F\text{I}_{O_2}$ 0.1 + ASA + propofol	0	7	0	0

either a zero or a second-order polynomial (table III). The best fit for SAP/$\dot{Q}$ plots was either a zero or a first-order polynomial, with frequent (up to four of eight or three of seven dogs) second-order polynomials in some of the experimental situations (table IV).

Hypoxia

Hypoxia decreased arterial and mixed venous $P\text{O}_2$, and arterial $P\text{CO}_2$ (tables I, II). Haemodynamic changes induced by hypoxia were an increase in $\dot{Q}$, SAP and PAP at uncontrolled flow and an increase in PAP at the lowest flow in both the responders and the non-responders (tables I, II). Hypoxia increased PAP at all values of $\dot{Q}$ studied in the responders (fig. 1). This effect of hypoxia was not significant when assessed on composite PAP/$\dot{Q}$ plots in "non-responders" (not shown). Hypoxia did not significantly affect composite SAP/$\dot{Q}$ plots (figs 2, 3).

TABLE IV. *Best fit for systemic arterial pressure–cardiac output relationships in hyperoxic and hypoxic dogs before and after administration of propofol*

	Polynomial order			
	Zero	First	Second	Third
Responders ($n = 8$)				
$F\text{I}_{O_2}$ 0.4	6	2	0	0
$F\text{I}_{O_2}$ 0.1	2	2	4	0
$F\text{I}_{O_2}$ 0.4+propofol	3	3	1	1
$F\text{I}_{O_2}$ 0.1+propofol	1	7	0	0
Non-responders ($n = 7$)				
$F\text{I}_{O_2}$ 0.4	3	1	3	0
$F\text{I}_{O_2}$ 0.1	0	5	2	0
$F\text{I}_{O_2}$ 0.4+ASA	4	2	1	0
$F\text{I}_{O_2}$ 0.1+ASA	1	5	1	0
$F\text{I}_{O_2}$ 0.4+ASA+propofol	4	3	0	0
$F\text{I}_{O_2}$ 0.1+ASA+propofol	1	6	0	0

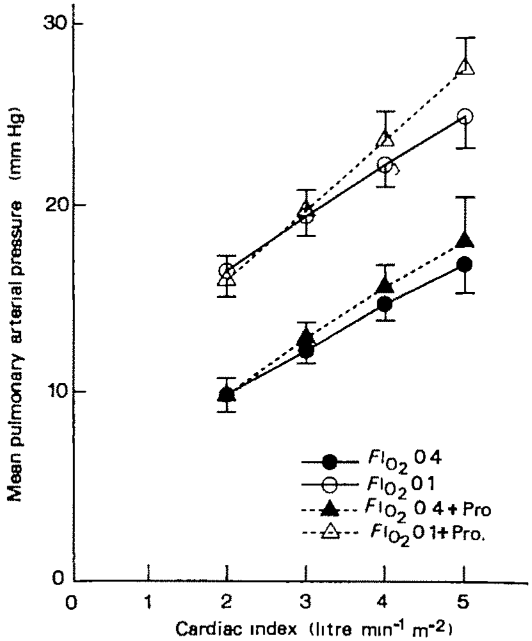

FIG. 1. Composite plots of mean pulmonary arterial pressure (PAP) (mean (SEM)) *v.* cardiac output ($\dot{Q}$) for eight responder dogs during hyperoxia ($F\text{I}_{O_2}$ 0.4) and hypoxia ($F\text{I}_{O_2}$ 0.1) before and after propofol (Pro.) 18 mg kg⁻¹ min⁻¹ i.v. Propofol did not affect PAP at any value of $\dot{Q}$ during hyperoxia or hypoxia.

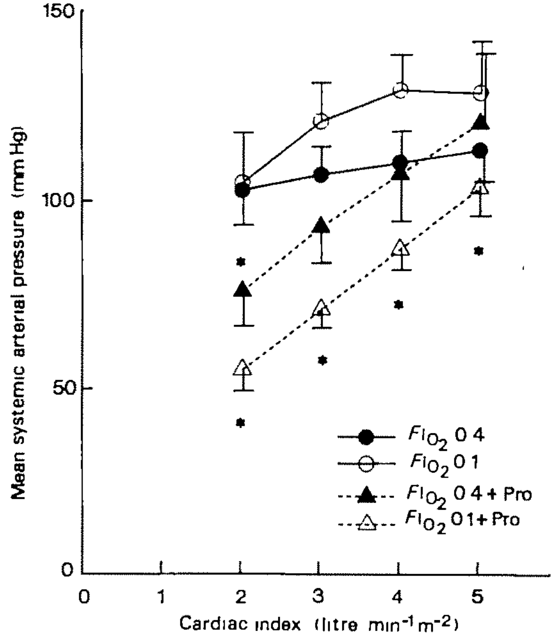

FIG. 2. Composite plots of mean systemic arterial pressure (SAP) (mean (SEM)) *v.* cardiac output ($\dot{Q}$) for eight responder dogs during hyperoxia ($F\text{I}_{O_2}$ 0.4) and during hypoxia ($F\text{I}_{O_2}$ 0.1) before and after propofol (Pro.) 18 mg kg⁻¹ min⁻¹ i.v. *$P < 0.05$ compared with control without propofol at the same $F\text{I}_{O_2}$. Propofol decreased SAP at the lowest $\dot{Q}$ in hyperoxia and at all values of $\dot{Q}$ during hypoxia.

Cyclo-oxygenase inhibition by acetylsalicylic acid

Administration of ASA 1 g i.v. to the non-responders had no effect at $F\text{I}_{O_2}$ 0.4, but increased PAP and SAP (the latter at the lowest $\dot{Q}$ only) at $F\text{I}_{O_2}$ 0.1 (table II). A pulmonary pressor response was restored over the entire range of $\dot{Q}$ studied (fig. 4). Composite SAP/$\dot{Q}$ plots were unaffected by ASA (not shown).

Propofol

In the responders, propofol decreased arterial $P\text{O}_2$ and mixed venous $P\text{O}_2$ (the latter at $F\text{I}_{O_2}$ 0.1

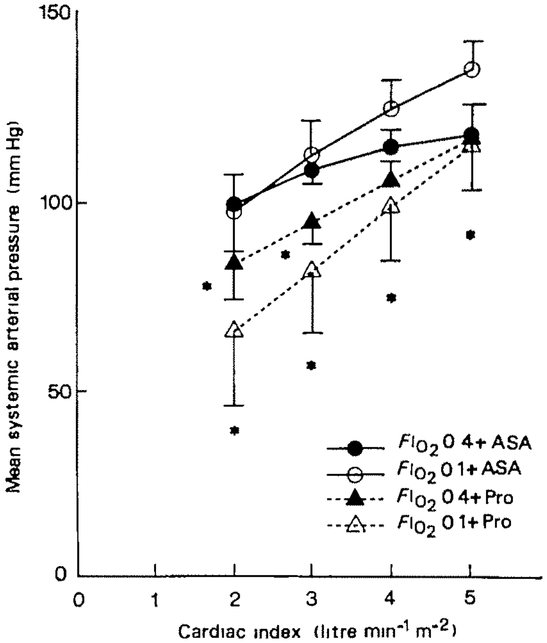

FIG. 3. Composite plots of mean systemic arterial pressure (SAP) (mean (SEM)) v cardiac output ($\dot{Q}$) for seven non-responder dogs treated with acetylsalicylic acid (ASA) 1 g i.v. during hyperoxia ($F_{I_{O_2}}$ 0.4) and during hypoxia ($F_{I_{O_2}}$ 0.1) before and after propofol (Pro.) 18 mg kg^{-1} min^{-1} i.v. $^*P < 0.05$ compared with control without propofol at the same $F_{I_{O_2}}$. Propofol decreased SAP at the lowest $\dot{Q}$ during hyperoxia and at all values of $\dot{Q}$ during hypoxia

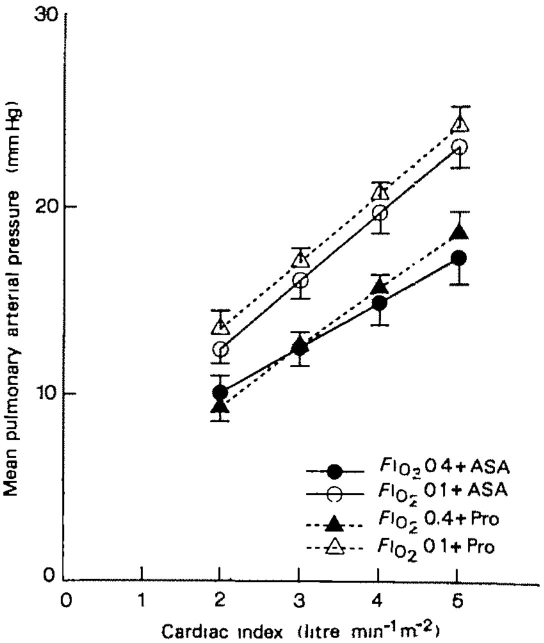

FIG 4. Composite plots of mean pulmonary arterial pressure (PAP) (mean (SEM)) v cardiac output ($\dot{Q}$) for seven non-responder dogs with hypoxic vasoconstriction restored by acetylsalicylic acid (ASA) 1 g i.v. during hyperoxia ($F_{I_{O_2}}$ 0.4) and during hypoxia ($F_{I_{O_2}}$) 0.1) before and after propofol (Pro.) 18 mg kg^{-1} min^{-1} i.v. Propofol did not affect PAP at any value of $\dot{Q}$ during hyperoxia or hypoxia

only). In the non-responders, propofol decreased arterial and mixed venous P_{O_2} at $F_{I_{O_2}}$ 0.1. In both responders and non-responders, SAP was decreased at the lowest $\dot{Q}$ at $F_{I_{O_2}}$ 0.4 and at both the highest and the lowest $\dot{Q}$ at $F_{I_{O_2}}$ 0.1 (tables I and II). Propofol decreased heart rate, (except in hyperoxia after ASA), but did not affect $\dot{Q}$ when venous return was not manipulated. Over the entire range of $\dot{Q}$ studied, propofol did not affect PAP (figs 1, 4), but decreased SAP at the lowest $\dot{Q}$ during hyperoxia and at all values of $\dot{Q}$ during hypoxia (figs 2, 3). Replacing PAP by (PAP−PCWP) and SAP by (SAP−RAP) did not affect the significance of any of the observed changes in pressure/$\dot{Q}$ plots after propofol.

Plasma concentrations of propofol

Plasma concentrations of propofol in three responders and in three non-responders were stable (*F* ratio of the analysis of variance, $P > 0.05$) and averaged 5.1 (0.4) μg ml^{-1} at 20 min, 7.4 (0.5) μg ml^{-1} at 40 min, 5.8 (0.5) μg ml^{-1} at 60 min, 6.2 (0.5) μg ml^{-1} at 80 min and 6.6 (0.5) μg ml^{-1} at 100 min after starting the continuous infusion.

DISCUSSION

In this experimental model propofol had no effect on pulmonary vascular tone, but markedly reduced systemic vascular tone during hypoxia and when cardiac output was decreased.

Systemic and pulmonary vascular tone are evaluated commonly by SVR and PVR calculations. This approach, derived from Poiseuille's law on laminar flows of Newtonian fluids in straight circular tubes, rests on the assumptions that both (SAP−RAP)/$\dot{Q}$ and (PAP−PCWP)/$\dot{Q}$ relationships are linear and pass through the origin. However, when the (arterial minus venous pressure divided by flow) relationship is non-linear or does not pass through the origin, isolated resistance calculations cannot discriminate between active (tone-dependent) and passive (flow-dependent) changes in arterial pressure [9].

In the present study, PAP/$\dot{Q}$ plots were found to be essentially linear, confirming previous studies of isolated lungs [8, 16] and of intact pentobarbitone-anaesthetized [10, 11] or conscious [17, 18] dogs. As can be inferred from PCWP values at high and at low $\dot{Q}$ (tables I, II) and from the composite PAP/$\dot{Q}$ plots (figs 1, 4), extrapolated pressure intercepts of (PAP − PCWP)/$\dot{Q}$ plots were equal or close to zero in hyperoxia, but positive in hypoxia and this is also in agreement with previous reports [10, 11, 17, 18]. If one accepts the validity of extrapolation of pressure–flow plots (measurements at very low flows cannot be obtained in intact animals), the (PAP − PCWP)/$\dot{Q}$ relationship may be independent of the absolute value of PAP and $\dot{Q}$ in hyperoxic and in zone-3-perfused lungs, and pulmonary vascular tone assessed correctly by calculated PVR. Our results suggest that this is not so in hypoxia, and confirm that evaluation of pulmonary vascular tone is better by PAP measurements at several flows [9].

The lungs of our recumbent dogs were probably perfused in zone 3 at uncontrolled flow and presented a progressively increasing proportion of zone 2 when $\dot{Q}$ was decreased. At the greatest $\dot{Q}$, PCWP would be equal to left atrial pressure, but at the smallest $\dot{Q}$, PCWP would lie between alveolar pressure and closing pressure [18, 19] It is also possible that, during hyperoxia and at the highest flow, PAP would be increased by a left atrial pressure (and thus also PCWP) higher than closing pressure, while PCWP would most likely be lower than closing pressure at the lowest flow [20]. However, during hypoxia, the composite PAP/$\dot{Q}$ plots (figs 1, 4) had extrapolated pressure intercepts higher than PCWP at the greatest flow, which may suggest that PCWP could remain lower than closing pressure at all flows. As the effective outflow pressure, or closing pressure, cannot be measured in intact animals, and as PCWP or left atrial pressure cannot be taken as this effective outflow pressure, we decided to evaluate pulmonary vascular tone by PAP/$\dot{Q}$ instead of by (PAP − PCWP)/$\dot{Q}$ plots, being aware that the slope and the extrapolated pressure intercepts of the PAP/$\dot{Q}$ plots are probably influenced by left atrial pressure in hyperoxia.

Over the range of $\dot{Q}$ studied, SAP/$\dot{Q}$ relationships in the present experiments also were found most frequently to be linear, but best fits as second- and even third-order polynomials were encountered more often. In pentobarbitone-anaesthetized dogs after baroreceptor denervation [21, 22] or at controlled carotid sinus pressures [8] (open loop), SAP/flow plots have been reported to be either close to linear [21, 22] or curvilinear with best fits in steady state as a third-order polynomial [8]. In these studies, extrapolated pressure intercepts were either close to RAP [20, 21] or definitely higher [8]. Under more natural conditions of an intact baroreflex (closed loop), SAP/flow curves have constantly been found to be curvilinear, with a convexity to the pressure axis at low flow [8, 21, 22]. In our dogs, when venous return was reduced progressively, SAP tended to remain constant until $\dot{Q}$ reached values of 2–2.5 litre min^{-1}, as was also previously noted in conscious normoxic dogs [17]. It has been suggested that the flow autoregulation (a progressive change of SAP at a given flow) that occurs in the systemic vascular bed would be affected by hypoxia (inspired or resulting from decreased flow at tissue level) [8, 23]. Over the range of $\dot{Q}$ studied in our experiments, SAP seemed to be higher at the highest $\dot{Q}$ in hypoxia compared with hyperoxia, but this was not significant. Nonetheless, in our dogs SAP/Q plots always were either non-linear or had extrapolated pressure intercepts higher than RAP, and thus calculated SVR would never be independent of the absolute values of pressure and flow. The only way, therefore, to evaluate systemic vascular tone correctly is to measure systemic vascular pressures over a wide range of flows.

In our dogs, propofol was infused at the upper limit of the range recommended for total i.v. anaesthesia in clinical practice, and this resulted in blood concentrations that were stable, although higher than required to maintain anaesthesia in man. Reductions in systemic arterial pressure of variable importance, accompanied or not by a decrease in cardiac output, according to dose, type of surgery and other anaesthetics given concomitantly, have been reported in several studies [1–7]. These systemic haemodynamic effects appear to be dose-dependent. In our dogs, propofol had a slight negative chronotropic effect, but otherwise did not affect any cardiovascular measurement at uncontrolled flow during hyperoxia. However, when venous return was reduced or hypoxia instituted, propofol decreased SAP at a given $\dot{Q}$, indicating a reduction in systemic vascular tone. Cyclo-oxygenase inhibition by ASA to enhance hypoxic pulmonary vasoconstriction did not affect the systemic vascular effects of propofol. It is of interest that no change in pulmonary vascular tone could be detected after propofol, which is another example [10] of a vasodilator with contrasting effects on pulmonary and systemic blood vessels.

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IS THERE A RELATIONSHIP BETWEEN MASSETERIC MUSCLE SPASM AND MALIGNANT HYPERPYREXIA?

A. S. CHRISTIAN, F. R. ELLIS AND P. J. HALSALL

SUMMARY

The occurrence of masseteric muscle spasm (MMS) in children is thought to be frequent and to be associated usually with malignant hyperpyrexia (MH). We have found a lower incidence of MMS in children and 50% had no muscle abnormality. Clinical features that support a diagnosis of MH include high serum creatine kinase (CK) concentration and the presence of myoglobinuria. There is evidence to suggest that suxamethonium does increase jaw tone in adults and children, and an exaggerated response may be taken clinically to be MMS. However, MMS should still be regarded as an early warning sign of MH.

Jaw rigidity or masseteric muscle spasm (MMS) following administration of suxamethonium has been described as the most common manifestation of an early reaction in malignant hyperpyrexia (MH) [1], making tracheal intubation difficult or impossible. In 1970, Britt and Kalow found that 80% of MH susceptible (MHS) patients who received suxamethonium developed muscle rigidity, although this did not relate only to MMS [2]. In 1984, we reported an incidence of 64% [3], and in 1986 Rosenberg and Fletcher [4] reported that 50% of MHS patients developed muscle rigidity. Schwartz, Rockoff and Koka [5] described a small series of children in whom there was a high incidence of MMS (just over 1 in 800). Surprisingly, all these cases occurred in a subgroup having induction of anaesthesia with halothane, producing an incidence of almost 1 in 100. No patient died and all those investigated were said to be susceptible to MH (100% incidence). The muscle biopsy used the calcium uptake technique described by Ryan [6], but this has since been discredited [7].

Carroll [8] reported an incidence similar to that of Schwartz: 1% of children having halothane induction of anaesthesia developed MMS, 2.8% when the child had concomitant strabismus. Only one patient with MMS was considered to be suffering from a possible MH reaction, but no patient had formal muscle biopsy screening for MH susceptibility. The incidence of MMS in patients having i.v. induction of anaesthesia was not given. If the incidence quoted by Rosenberg was applied to Carroll's study, there would be a prevalence of MH in children of 1 in 200, and 1 in 100 for children with strabismus. Clearly this is very much greater than that quoted usually—1 in 10–20000 [9].

We felt that the problem of MMS in children warranted further study in a much larger group of patients.

PATIENTS AND METHODS

We examined the records of all probands younger than 16 yr who had masseteric muscle spasm (MMS) as a presenting sign and who had been investigated by muscle biopsy using the European MH Protocol [10]. Patients were classified as MHS (susceptible), MHN (normal) or MHE (equivocal), as described by the Protocol Amendment [11]. MHE patients were reclassified as a consequence of further family studies. It is the policy of this Unit not to investigate children younger than 10 yr; these patients are investigated indirectly via their parents. If both parents were shown to be MHN, the proband was assumed to be MHN. If one parent was MHS, the proband was accepted as MHS. If a parent was MHE, the

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proband would be shown eventually to be MHS or MHN as further family studies proceed. The remaining MHE patients still require further elucidation from family studies.

The clinical histories of the MH reaction of all the probands were reviewed, noting age, sex, operation, premedication, details of anaesthesia including evidence of MMS, generalized muscle rigidity, core temperature and end-tidal carbon dioxide production. Laboratory investigations included creatine kinase (CK) and serum potassium concentrations, myoglobinuria and blood-gas values. Details of treatment and eventual outcome were recorded.

RESULTS

Sixty-six patients younger than 16 yr presented with MMS and, after laboratory screening, were classified initially as: 27 MHN, 28 MHS and 11 MHE. Six of the MHE patients were reclassified as MHS (a relative having been demonstrated to be MHS), producing 34 MHS and five MHE. Therefore 51% of probands presenting with MMS were shown to be MHS. These 66 probands represented 54% of all the probands investigated over a 6-yr period.

Demography

There was no significant difference between the groups regarding age, but the older children were MHS and younger ones MHN ($P < 0.01$) (fig. 1). There was no proband younger than 2 yr.

The male : female ratio in the MHN group was over 4 : 1 (table I) ($P < 0.01$). Table I also shows the types of operation during which MMS occurred.

Clinical presentation

Of the 66 patients, 25 had no other signs of MH recorded; 12 were MHS, 13 MHN and none MHE. Two of the remaining MHN patients were shown to have evidence of myopathy and, other than MMS, their only other presenting sign was a minimal increase in temperature and a marked increase in CK concentration which was present also at rest in one of these patients.

In the majority of the children, surgery and anaesthesia were abandoned, so that the severity of the MH reaction was difficult to assess. However, only one MHS patient showed fulminant signs which resolved with symptomatic therapy only, without recourse to dantrolene or cooling. One MHN patient showed a more

TABLE I. *Demographic details of patients studied.* *P < 0.01

	MHS ($n = 34$)	MHN ($n = 27$)	MHE ($n = 5$)
Sex distribution			
Male	17	22	4
Female	17	5*	1
Operation when MMS occurred			
E N.T	20	12	—
Congenital (ortho + plastic)	3	4	1
Dental	3	2	—
Trauma/acute	5	1	1
Ophthalmic	3	4	1
Other	—	4	2

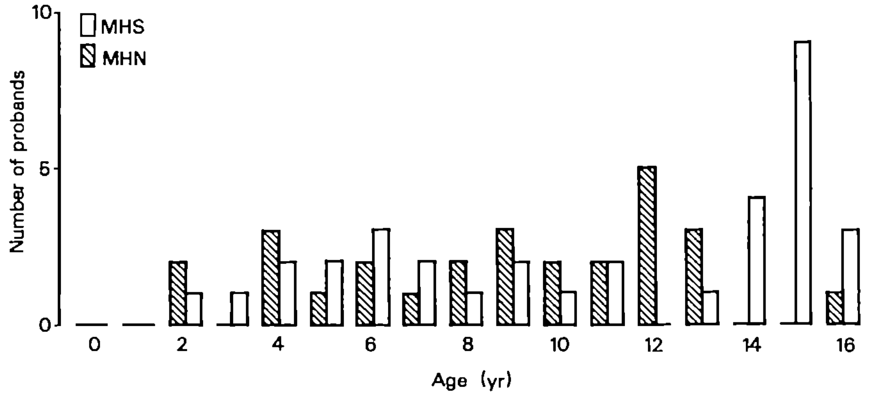

FIG. 1. Histogram showing the ages of both MH susceptible (MHS) and MH normal (MHN) probands presenting with masseteric muscle spasm (MMS).

TABLE II. *Features in the patients studied *Two probands with myopathy; †one proband with arthrogryposis; ‡one proband with myopathy*

	MHS ($n = 34$)	MHN ($n = 27$)	MHE ($n = 5$)
No other signs	12	13	0
Mild signs (heart rate > 150 beat min^{-1} + pyrexia < 38.5 °C)	13	7*	2
Fulminant	1	1†	0
EMG assessment	5	9‡	1

TABLE III *Anaesthesia and treatment used*

	MHS ($n = 34$)	MHN ($n = 27$)	MHE ($n = 5$)
Premedication	19	11	—
Induction			
I.v.	13	3	3
Inhalation	13	26	2
Abandoned	17	11	3
Continued	3	3	—
Cooled	1	1	—
Dantrolene	1	2	—
Correction of acidosis	1	1	—

TABLE IV. *Plasma creatine kinase concentrations (mean (SD)) and presence of myoglobinuria* *P < *0.01.* †n = *No. tested*

	MHS ($n = 34$)		MHN ($n = 27$)	MHE ($n = 5$)
CK concn (iu litre^{-1})				
Reaction	13414 (20085)	ns	3760 (8527)	38868 (82259)
Resting	147 (82)	*	85 (43)	149 (47)
No. with myoglobinuria	7 ($n = 11$)		2 ($n = 10$)	2 ($n = 2$)

marked reaction, but suffered also from arthrogryphosis multiplex (table II). The majority of the remaining patients showed minor increases in temperature and heart rate, occasionally with ventricular ectopic beats. Of the 15 patients who had an EMG, all were normal, with the exception of one of the myopathic patients (the other did not have an EMG).

Anaesthesia and treatment (table III)

There were no fatalities recorded and there was no significant continuing morbidity.

I.v. induction of anaesthesia was more common in the MHS group and inhalation induction more common in the MHN group ($P < 0.01$). In most patients the procedures were abandoned and they did not receive any treatment other than careful monitoring and, in two subjects, correction of acidosis.

Serum creatine kinase (CK) and myoglobinuria

In the MHS group the presence of an increased CK concentration (> 1500 iu litre^{-1}) was more common than in the MHN group, even when no other sign was apparent (ns). Conversely, three MHS probands had no marked increase in CK concentration, or other signs. There was no significant difference between the groups for CK values obtained during the reaction because of a large range of values (table IV). However, although resting CK values were significantly different between the MHS and MHN groups ($P < 0.01$), there was a large overlap, confirming previous observations that resting CK concentration is unhelpful as a sole predictor of MH [12].

Myoglobin was measured infrequently, but in the MHN group myoglobinuria was present only in the two patients shown subsequently to have a myopathy.

DISCUSSION

It is difficult to determine the incidence of masseteric spasm in children because of lack of information on the total number of general anaesthetics given to children in the U.K. However, 66 reported cases of MMS over a period of about 6 yr in the U.K., during which time we estimate there have been 5 million anaesthetics given to children, gives an apparent incidence of 1 in 100000. This is a value one-hundreth of that reported by Schwartz and colleagues in Boston, U.S.A. [5].

This difference raises the question of whether or not the Boston group and ourselves are reporting the same condition. We define MMS as a clinically obvious increase in jaw tone which interferes with passive movements of the jaw. However, the difference between these studies is that Schwartz and colleagues were actively looking for MMS, whereas we relied on referrals by anaesthetists who felt that MMS was of such a degree that it merited further investigation.

The Schwartz study was criticized at the time of its publication because of the possibility that the incorrect *in vitro* test had been applied [13, 14]. Later, Muldoon's laboratory showed that there was no evidence to support the use of the calcium uptake technique for the diagnosis of MH [6]. Thus the apparently high incidence of MH in the MMS group reported by Schwartz cannot be substantiated.

Our study differed from the American survey in two important ways: first, MMS occurred throughout the whole age range 2–16 yr, with a tendency for the younger group to be MHN and the older group MHS, whereas the Schwartz group reported no occurrence in subjects older than 10 yr. Second, MMS was more likely to result from MH if an i.v. induction had been used, whereas most of the probands who developed MMS following an inhalation induction were MHN; in the Schwartz study MMS occurred almost invariably with inhalation induction.

Premedication, which has been thought to delay or abort an MH reaction, did not reduce the incidence; 80% of premedicated children were MHS.

The differences in the sex distribution are interesting, MHS being distributed equally, whereas MHN occurred more frequently in males. There is usually a strong male preponderance in probands of all ages [15]. An explanation may be that, in the present survey, ENT operations were the most common surgical procedure whereas previously we have reported that trauma is the most common procedure, and it is likely that more males present for trauma surgery.

This study has shown that a significant proportion of patients who developed MMS were susceptible to MH on muscle biopsy testing using the European Protocol; thus there is a strong relationship between MMS and MH. However, because anaesthesia was usually abandoned, other supportive evidence was often unavailable, even in the MHS probands. The duration of the spasm should be recorded. The other clinical signs which seemed to be valuable were the initial and 24-h CK values and the presence of myoglobinuria. These are measurements which should be available even when anaesthesia has been abandoned. Even though there was no significant difference in CK concentrations between the MHS and MHN groups, because of the wide range of values obtained an increased value was found more commonly in the MHS probands.

The reason for the development of MMS, without any apparent underlying abnormality, requires an explanation. VanDerSpek and coworkers have shown that all children receiving suxamethonium respond with a reduction in mouth opening and an increase in jaw stiffness [16]. More recently, Leary and Ellis have shown that jaw tone is increased for a short period (less than 1 min) following suxamethonium in 85% of adults [in preparation]. From these studies, an increased masseteric muscle tone can be assumed to be a normal event after suxamethonium and is dose-related [Leary and Ellis, personal communication]. The more severe examples could be described as MMS. Thus the MMS group could represent an extreme of a normal distribution. There is, therefore, an unresolved disparity between this and the bimodal distribution of MH in the population.

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VENOUS SEQUELAE FOLLOWING I.V. ADMINISTRATION OF DICLOFENAC

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SUMMARY

Diclofenac sodium (Voltarol) was administered i.v. to 149 consecutive patients who were thought likely to benefit from its anti-inflammatory action. Patients were allocated randomly to one of two groups: group A received the undiluted i.m. preparation (25 mg ml^{-1}) and group B the i.m. preparation diluted in normal saline (5 mg ml^{-1}). Diclofenac 1 mg kg^{-1} administered over a 10-min period via a 23-gauge needle into a vein at either the antecubital fossa or the dorsum of the hand. No local or systemic problems were encountered in either group, at the time of injection. A high incidence of painless local venous thrombosis occurred in both hand and arm veins, 72 h after administration in group A (85% and 58%, respectively). The incidence of thrombosis was reduced markedly after administration of the diluted drug: 38% hand veins; 8% antecubital fossa veins.

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID). The data sheet for the parenteral formulation states that the drug is for i.m. use only and the i.v. route is not recommended by the manufacturers, not because of specific problems, but because of lack of an adequate body of information regarding this route. The i.v. route has been used by others with few ill effects [1, 2]. Diclofenac is poorly water soluble, so that 1,2-propylene glycol is used as a solvent. The standard i.m. preparation also contains benzyl alcohol and mannitol. The osmolarity of the solution is the same as that of blood and the pH is in the range 8.1–8.9 (usually 8.7) [Ciba-Geigy Pharmaceuticals, personal communication].

Although it is used frequently in the management of arthritis and musculo-skeletal disorders, diclofenac is also advocated for use in pain following minor surgery [3]. As peak plasma concentrations do not occur for 30 min after i.m. injection [4], we explored the efficacy of administration by the i.v. route. The administration of the drug to produce high plasma concentrations before surgery should inhibit prostaglandin synthesis before the tissue disruption of surgey and therefore reduce the intensity of postoperative pain.

The aim of this study was to determine if diclofenac could be administered i.v. without local venous sequelae.

PATIENTS AND METHODS

We studied 160 patients (ASA grades I and II) (age range 17–64 yr). Those patients suffering from asthma, allergies, aspirin intolerance and bleeding disorders were excluded, as were those with a history of peptic ulcer or renal or hepatic impairment. The population included patients undergoing minor orthopaedic, plastic and general surgery. Approval was granted by The Research Ethics Committee, Queens University, Belfast and informed verbal consent was obtained from all patients.

Patients were allocated randomly to receive diclofenac 1 mg kg^{-1} as solutions of either 25 mg ml^{-1} (group A) or 5 mg ml^{-1} (diluted in 0.9% saline) (group B) into a hand or antecubital fossa vein. The standard i.m. formulation of diclofenac was used in each group. Although diluting this formulation does not cause clouding, the solution becomes unstable and so was used immediately after preparation. Injection was made via a 23-gauge Butterfly needle, over a 10-min period. As the drug was injected subjects were asked "How

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does that feel?". The needle was then removed and a firm dressing applied over the site. Anaesthesia was induced with thiopentone 5 mg kg^{-1} via another (distant) vein in the same limb.

Following induction of anaesthesia and for 1 h after injection of diclofenac, the veins were observed for local reaction. Observations were made also at 24 and 72 h for erythema, tenderness, phlebitis and thrombosis.

RESULTS

Eleven of the 160 patients originally included in the study were lost to follow-up and their data have been omitted from the results. Mean age and sex were similar in the groups (table I). Neither pain nor local reaction occurred at the injection site during the first 1 h following administration of diclofenac.

A similar incidence of venous sequelae was noted in males and females in both groups. Venous sequelae were limited to painless thrombosis only, this being evident by 24 h ($n = 47$, group A; $n = 14$, group B). Seventy-two hours after injection there were seven further cases of thrombosis in group A and three further cases of thrombosis in group B. The thrombosis rate on the 3rd day was less (8% *v.* 85%) in the group receiving diluted drug administered via an antecubital fossa vein rather than undiluted drug via the veins on the dorsum of the hand (table II).

TABLE I. *Demographic data*

	Group A (25 mg ml^{-1})		Group B (5 mg ml^{-1})	
	Hand	Arm	Hand	Arm
Mean age (SD) (yr)				
Male	28.1 (9.9)	32.3 (12.4)	26.8 (6.9)	35.6 (11.9)
Female	27.5 (9.8)	26.6 (11.1)	28.8 (13.7)	30.9 (14.8)
No. males	21	17	18	21
No. females	18	19	19	16
Total number	39	36	37	37

TABLE II. *Incidence of thrombosis following i.v. administration of diclofenac*

	Group A (25 mg ml^{-1})		Group B (5 mg ml^{-1})	
	Hand	Arm	Hand	Arm
Total number of patients	39	36	37	37
No. with thrombosis				
Day 1	27	20	12	2
Day 3	33	21	14	3
Percent with thrombosis				
Day 3	85	58	38	8

The incidence of venous thrombosis was higher in the hand than in the antecubital fossa veins when the dilute solution was used: 38% compared with 8% ($P = 0.006$, chi-square test). This was also so with group A (25 mg ml^{-1}), the incidence being 85% and 58%, respectively ($P = 0.02$). Pooling data from groups A and B confirmed a significant difference in the incidence of thrombosis at the two sites ($P = 0.001$).

The incidence of thrombosis was markedly less in the hand veins with the dilute solution compared with the 25-mg ml^{-1} concentration ($P < 0.001$). This was also the case when the drug was administered by large veins in the antecubital fossa ($P < 0.001$).

DISCUSSION

The NSAID have been used successfully for management of postoperative pain [5]. Acute pain is perceived when nociceptor stimulation occurs as a result of trauma which releases many substances, including prostaglandins [6]. Prostaglandins lower the neurophysiological threshold to pain, leading to hyperalgesia. The ability of NSAID to inhibit prostaglandin synthesis converts this hyperalgesic state to normal algesia.

The use of NSAID before operation should, theoretically, be more effective than postoperative administration, and has successfully controlled postoperative pain in patients undergoing the removal of impacted third molar [7]. Despite attempts to premedicate patients with NSAID before surgery, peak plasma concentrations may not be achieved consistently at the time of operation. The i.m. preparation of diclofenac could be used, but 30 min should lapse to allow peak plasma concentrations to be attained and the injection is painful.

The i.v. administration of diclofenac has been investigated by Rainer and Klein, in 36 patients suffering from rheumatoid arthritis [1]. No adverse clinical or haematological effects were noted when diclofenac 75 mg in physiological saline 250–500 ml was infused over 30 min. Willis and colleagues also administered diclofenac i.v. to seven volunteers [2], each subject receiving diclofenac 50 mg in 2 ml over 2 min and subsequently

50 mg of aqueous solution by mouth to study the pharmacokinetics of the drug.

The diclofenac preparation studied contains the solvent 1,2-propylene glycol, and this probably played a major role in the development of venous thrombosis. Diazepam is dissolved in the same solvent and this preparation has a high incidence of venous sequelae [8–10]. Graham, Pagano and Conner [8] observed that an 87% incidence of pain on injection with undiluted diazepam was reduced to 12% by dilution to 20 ml, the incidence of thrombophlebitis decreasing to 8%. A dilution to approximately 20 ml (5 × dilution) was considered practical in our study.

Mattila and colleagues also observed venous problems following the use of diazepam in propylene glycol [9]: they observed an incidence of thrombophlebitis in hand veins of 62.2%, 14 days after injection. Schou Olesen and Huttel studied the incidence of local reactions in hand and wrist veins following i.v. administration of diazepam in various solvents, including propylene glycol and lipid emulsion [10]. Pain during injection and thrombophlebitis at 24 h occurred most frequently with the propylene glycol preparation (78% and 48%, respectively) and least frequently with the lipid emulsion (1% and 4%, respectively). We did not observe any pain on injection, despite questioning, with either the standard or dilute solution if diclofenac.

Water soluble drugs do not appear to produce such a high incidence of venous sequelae. In their study of diazepam, Graham and colleagues used a control group of 240 patients who received either fentanyl or morphine. The incidence of pain on injection and thrombophlebitis was 2% and 1%, respectively [8].

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ELECTROENCEPHALOGRAPHIC EFFECTS OF LAUDANOSINE IN AN ANIMAL MODEL OF EPILEPSY

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SUMMARY

We examined the effects of laudanosine, one of the principal metabolites of atracurium, on the electroencephalogram (EEG) in an animal model of induced epilepsy. Fourteen rabbits were anaesthetized with 4% halothane in oxygen, the trachea intubated and the lungs ventilated mechanically with 30% oxygen and 1% halothane in nitrogen. Animals were assigned randomly to receive either an infusion of laudanosine (laudanosine group, n = 7) at a rate calculated to produce plasma concentrations similar to those found following the clinical use of atracurium, or an equal volume of normal saline (control group, n = 7). To induce an epileptogenic focus, gelfoam sponges soaked in a pH-adjusted 4% cefazolin solution were applied bilaterally to the parietal cortical surface. This resulted in the production of spike and burst EEG activity in all animals. However, scoring the frequency of the spikes and bursts revealed no significant differences between the laudanosine and control groups. We conclude that, in this animal model of epilepsy, no increased incidence of seizure activity was produced by mean plasma laudanosine concentrations as great as 0.8 μg ml^{-1}. These results suggest that the routine use of atracurium is unlikely to provoke seizures, even in the presence of an epileptogenic focus.

Atracurium is a non-depolarizing neuromuscular blocking agent of intermediate duration which is used widely during surgical procedures for which muscle paralysis is indicated. Atracurium is not only metabolized by ester hydrolysis, but also degrades spontaneously in the body by Hofmann elimination at physiological pH and temperature [1]. Because the offset of the action of this drug is independent of liver or kidney function, atracurium may be the preferred neuromuscular blocking agent for patients with hepatic or renal insufficiency. One of the principal metabolites of atracurium, laudanosine [1,(3′,4′-dimethoxy benzyl)2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline], is a known central nervous system (CNS) stimulant [2, 3]. Laudanosine has been shown to cause seizures in animals only at plasma concentrations which greatly exceed those expected following the routine clinical use of atracurium [4]. It is not known, however, if clinically relevant concentrations of laudanosine could provoke seizure activity in patients with pre-existing cerebral pathology (brain tumour, trauma, epileptogenic focus). We therefore examined electroencephalographic effects of laudanosine in an animal model of induced epilepsy.

MATERIALS AND METHODS

Fourteen New Zealand White rabbits weighing 2.5–3.9 kg were studied following approval by the Animal Care Committee. They were initially anaesthetized with 4% halothane in oxygen. Following paralysis with pancuronium 0.3 mg kg^{-1} i.v. the trachea was intubated orally and the lungs ventilated mechanically with 30% oxygen and 1.0–1.5% halothane in nitrogen. Tidal volume and rate of ventilation were adjusted to 15 ml kg^{-1} and 30 b.p.m., respectively. The Pa_{CO_2} was maintained at 4.7–6.0 kPa through the addition of carbon dioxide to the inspired gas mixture. Oeso-

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phageal temperature was maintained at 37.5 °C through the use of a servo-controlled infra-red lamp and a heating pad. Catheters were inserted into the femoral artery and vein for the continuous monitoring of arterial pressure, intermittent sampling of arterial blood, and for the continuous infusion of normal saline 4 ml kg^{-1} h^{-1} and pancuronium 0.5 mg h^{-1}. The animals were then placed in the "sphinx" position and the head fixed in a stereotaxic frame. The scalp was incised in the midline and muscles were reflected laterally to expose the skull. All the incision sites were infiltrated subcutaneously with 0.25% bupivacaine. Brass screw electrodes were placed bilaterally in the skull over the frontal and occipital regions for the extradural recording of the cortical electroencephalogram (EEG) (Model 78, Grass Instrument, Quincy, MA). Biparietal craniectomies (approximately 4 mm in diameter) were made for the later application to the cortical surface of gelfoam sponges. The dural membrane under each craniectomy was carefully incised with a surgical blade to avoid injury to the underlying cortex.

Following the completion of the surgical preparation, the end-tidal halothane concentration was decreased to 1.0% and maintained at this value for at least 10 min before the control EEG recordings (C1) were made. The animals were then assigned randomly to receive either a loading infusion of laudanosine (Aldrich Chemical Co., Milwaukee, WI) at 96 μg kg^{-1} min^{-1} (laudanosine group) or an equal volume of normal saline (control group) for a period of 10 min. The EEG was again recorded (C2) and 4% cefazolin-soaked sponges (4 mm diameter, 1 mm thick) were applied bilaterally to the cortical surface. The pH of cefazolin solution was titrated to 7.20–7.30 with NaOH 0.1 mol $litre^{-1}$. The rate of infusion of laudanosine (or the same volume of normal saline) was simultaneously decreased to 24 μg kg^{-1} min^{-1}, and continued for the remainder of the experiment. Based upon the pharmacokinetic data of Shi and colleagues [2], this infusion regimen was expected to produce plasma laudanosine concentrations of approximately 0.8 μg ml^{-1}. Repeated recordings of the EEG and blood-gas analyses were made at 5, 10, 20, 30, 45 and 60 min following application of the cefazolin. Plasma samples were obtained at 20 and 60 min after the application of cefazolin from four laudanosine animals for the determination of laudanosine concentration by ion-exchange liquid chromatography [5]. Arterial blood-gas tensions and pH were measured by appropriately calibrated electrodes at 37 °C (IL-813, Instrumentation Laboratory, Lexington, MA). EEG were subsequently scored in a blinded fashion for the frequency of spike and burst activity. Spikes were defined as sharp wave activities with an amplitude greater than or equal to twice that of the background EEG. Bursts were defined as a continuous run of three or more spike waves.

Changes in physiological variables were examined within each group using a repeated measures analysis of variance, while comparisons between groups were examined with unpaired *t* tests. EEG scores were examined using a two-factor repeated measures analysis of variance. In addition, mean values for spike and burst frequency over time were calculated for each animal and intergroup comparisons were made using an unpaired two-tailed *t* test. Significance was assumed at $P < 0.05$.

RESULTS

There were no significant differences between or within the two groups in terms of arterial pressure, blood-gas values (table I), or oesophageal temperature at any point during the experiment. In both groups, spike activity developed within 5 min after cefazolin sponges were applied to the

TABLE I. *Mean (SD) values of physiological variables obtained before and 60 min after application of cefazolin. There were no differences between groups*

	Time C2		Time 60 min	
	Control	Laudanosine	Control	Laudanosine
MAP (mm Hg)	79 (7)	81 (5)	78 (5)	80 (6)
pH	7.41 (0.04)	7.41 (0.04)	7.40 (0.07)	7.41 (0.04)
Pa_{CO_2} (kPa)	5.3 (0.5)	5.3 (0.4)	5.2 (0.7)	5.1 (0.4)
Pa_{O_2} (kPa)	24.3 (1.5)	22.7 (2.7)	24.1 (1.2)	22.8 (2.7)

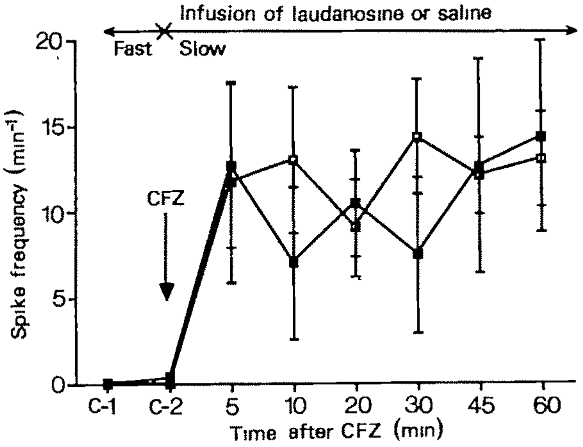

FIG 1. Mean (SEM) frequency of spike activity in the EEG of control (☐) and laudanosine (■) groups Arrow indicates the application of cefazolin (CFZ) to the cortex. Laudanosine or the same volume of normal saline were infused at a rapid (96 µg kg^{-1} min^{-1}) and then a slow rate (24 µg kg^{-1} min^{-1}).

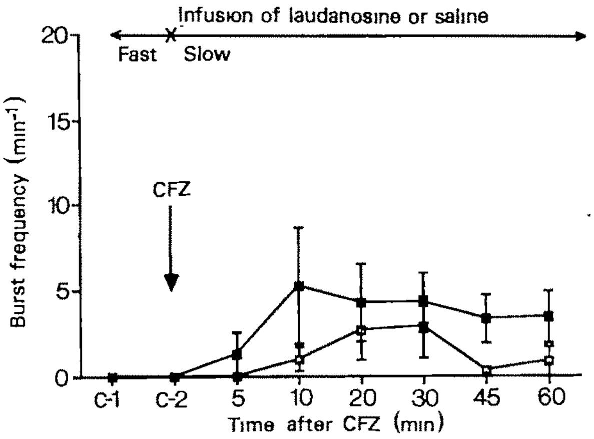

FIG. 2 Mean (SEM) frequency of burst activity in the EEG of control (☐) and laudanosine (■) groups Arrow indicates the application of cefazolin (CFZ) to the cortex Laudanosine or the same volume of normal saline were infused at a rapid (96 µg kg^{-1} min^{-1}) and then a slow rate (24 µg kg^{-1} min^{-1})

cortex, and continued throughout the experiment. The frequency of burst activity increased and peaked between 10 and 30 min in both group (figs 1, 2). However, there were no significant differences between the control and laudanosine groups in spike or burst frequency at any time point during the experiment, as revealed by analysis of variance. Analysis of mean spike and burst frequency showed no differences between the two groups ($P = 0.73$ and 0.09, respectively). Figure 3 shows a representative EEG pattern after the application of cefazolin. The infusion of laudanosine resulted in a mean plasma concentration of 0.83 (0.09) µg ml^{-1}.

DISCUSSION

Laudanosine has a long elimination half-life ($T_{\frac{1}{2}}$ = 200 min in man), and easily penetrates the blood–brain barrier [1, 6, 7]. The peak concentration of laudanosine in the cerebrospinal fluid was found to occur 5–10 min after a bolus

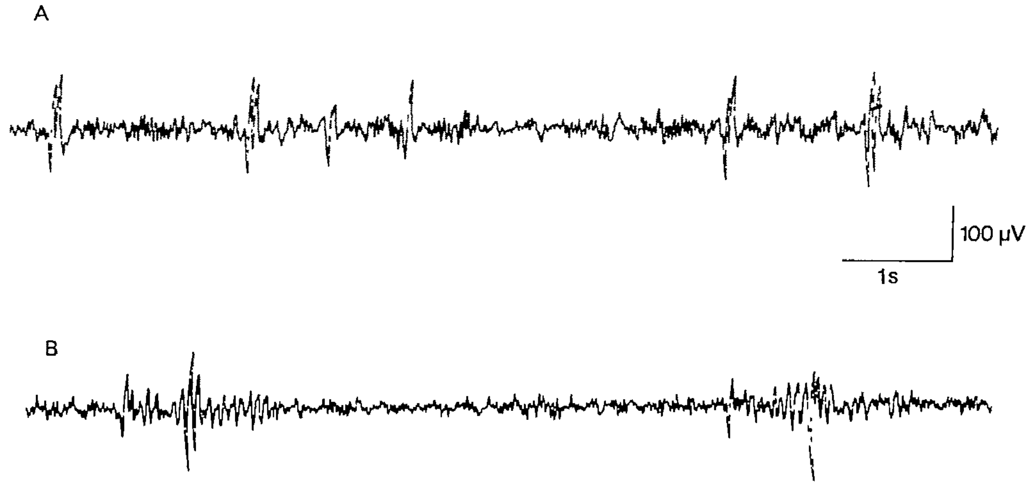

FIG. 3 Representative EEG changes induced by cefazolin A Spike wave activity 10 min after cortical application of cefazolin B Burst activity 20 min after cefazolin

injection, and varied between 36% and 87% of the corresponding plasma concentration [8]. In sufficient doses, laudanosine has been reported to produce convulsive movements or seizure activity on the EEG in a number of animal species [4, 9, 10]. An infusion of laudanosine 100 mg kg^{-1} h^{-1} caused convulsions in five awake rats (cumulative dose varied between 38.2 and 94.4 mg kg^{-1}), with the corresponding plasma laudanosine concentrations being greater than 20 μg ml^{-1} [4]. During the continuous infusion of laudanosine to halothane-anaesthetized dogs, a laudanosine concentration greater than 10 μg ml^{-1} induced EEG spikes, while concentrations greater than 17 μg ml^{-1} produced prolonged seizures (at cumulative doses of 30–50 mg kg^{-1}) [9]. Smaller doses (14–22 mg kg^{-1}) were reported to produce seizure activity on EEG in hyperventilated dogs [8]. In the majority of animal studies, the epileptogenic plasma concentration of laudanosine was at least eight times greater than that seen following the intraoperative use of atracurium. Even after 5–6 days of continuous neuromuscular block produced by an atracurium infusion to patients undergoing mechanical ventilation in an intensive care unit, the peak plasma concentration of laudanosine was 5 μg ml^{-1} and there was no evidence of cerebral excitation [11]. Renal function may have some role in excretion of unchanged laudanosine. Peak laudanosine concentrations after a single 0.5-mg kg^{-1} dose of atracurium were reported to be 0.327 and 0.758 μg ml^{-1} in normal and renal failure patients, respectively, although this difference was not statistically significant [12]. These concentrations are considerably lower than those reported with CNS excitation. However, despite these seemingly reassuring statistics, a question has remained as to whether or not patients with cerebral pathology are more sensitive to the epileptogenic effects of laudanosine.

To test this possibility, we assessed the EEG effects of clinically relevant concentrations of laudanosine in an established model of epilepsy. Laudanosine was infused in a manner which produced plasma concentrations of 0.8 μg ml^{-1}. This concentration may be seen following the routine intraoperative use of atracurium in patients with renal failure. The cerebral application of cephalosporin compounds has been shown to produce the behavioural and electrophysiological patterns of epilepsy [13]. The close relationship between the chemical structure of the cephalosporins and their epileptogenic activity has led to the assumption that those compounds promote the mechanisms of convulsive discharge of the neuronal cell membrane [14]. Cefazolin is known to possess potent epileptogenic properties and 2% and 4% solutions have been used to evaluate the anti-convulsant potential of the calcium channel blocker, nimodipine [15], the 4% solution producing a more intense epileptic activity than 2%. We used the more epileptogenic 4% concentration, and found that cortically applied cefazolin clearly produced EEG spikes and bursts. However, the frequencies of spikes and bursts were not significantly different between groups at any time, suggesting that laudanosine did not enhance seizure activity in this model. There was no apparent trend towards a difference between the groups in terms of spike frequency. Inspection of the burst data reveals that the mean number of bursts was slightly greater in laudanosine group at all times, although statistical significance could not be demonstrated at the 0.05 level of probability. Even if a statistical difference existed between groups in terms of burst frequency which was not apparent because of the relatively large standard errors in this study (type II error), the magnitude of the difference is not likely to have clinical importance. The mean number of bursts in the laudanosine group was greater by only approximately 2 min^{-1} compared with the control group. Sustained seizure activity was not observed in any of the laudanosine or control animals.

To our knowledge, these are the only data examining the propensity of laudanosine to activate epileptic activity in other than normal animals. These data, together with absence of case reports to the contrary despite the widespread usage of atracurium, cast doubt on the epileptogenic potential of clinically relevant plasma concentrations of laudanosine in the presence of excitable brain pathology.

In summary, in a topical antibiotic-induced epilepsy model, no increased incidence of seizure activity was detected in rabbits receiving laudanosine at rates sufficient to produce plasma concentrations similar to those seen following the clinical use of atracurium.

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Br. J. Anaesth. (1989), **62**, 553–559

EFFECT OF NICARDIPINE INFUSION ON THE RELEASE OF GLUTATHIONE S-TRANSFERASE FOLLOWING HALOTHANE ANAESTHESIA

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Liver dysfunction following exposure to volatile halogenated anaesthetics has long been established [1]. The role of halothane in the development of hepatic injury is the subject of renewed controversy and research. Significant increases in the plasma concentration of the hepatic cytosolic enzyme glutathione S-transferase B_1B_1 (GST) occur after halothane but not isoflurane anaesthesia [2, 3]. This led us to believe that measurement of GST in plasma could be valuable in the investigation of liver dysfunction following anaesthesia as the plasma concentrations of GST allow detection of minor and short-term hepatic injury which is not revealed using conventional hepatic enzymes [2, 3].

The role of calcium in mediating or propagating ischaemic cell injury, and the concept that increased concentrations of intracellular calcium constitute the final common pathway of cell injury have been reviewed [4]. Gelman and Van Dyke have propounded a similar "calciogenic" hypothesis for the development of liver toxicity associated with volatile anaesthetics [5]. Slow calcium channel blockers have a cell protective effect in ischaemic myocardial injury [6] and in ischaemic brain damage in rats [7]. Garay and co-workers [8] found that the calcium antagonist nicardipine might significantly reduce the extent of liver damage in rats after administration of the hepatotoxic agents carbon tetrachloride or d-galactosamine.

We have assessed the possibility that nicardipine given as an infusion before and during halothane anaesthesia in man might reduce the release of GST.

SUMMARY

To assess the possible protective effect of calcium channel blockade on hepatic function after halothane anaesthesia, 80 patients were allocated randomly to receive an i.v. infusion of either nicardipine or normal saline. Plasma concentration of glutathione S-transferase B_1 *subunits (GST) was measured as a sensitive index of hepatic damage. Data from 53 patients were analysed. Plasma GST concentration increased significantly at 3 and 6 h after induction of anaesthesia in the placebo group* ($P < 0.01$)*, and at 3 h* ($P < 0.01$) *and 6 h* ($P < 0.05$) *in the nicardipine group. The administration of nicardipine resulted in a greater increase in plasma GST concentrations at 3 h than did placebo* ($P < 0.05$)*, mainly because of a greater increase in males than in females. The increase in GST at 3 h was related inversely to plasma concentration of nicardipine both at the end of the exponential infusion* ($P < 0.01$) *and at 2 h after induction* ($P < 0.05$)*, when males had lower plasma nicardipine concentrations than females* ($P < 0.05$)*. Calcium channel blockade with nicardipine in the dose administered was not shown to reduce liver dysfunction after halothane anaesthesia.*

PATIENTS AND METHODS

Patients and samples

We studied patients aged 18–70 yr, ASA I or II [9], undergoing elective, peripheral orthopaedic surgery expected to last between 30 and 90 min. Ethics Committee approval and written informed consent were obtained. Patients who had undergone halothane anaesthesia within the preceding 3 months were excluded. Those patients receiving

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regular oral medication other than benzodiazepines or thiazide diuretics and those who gave a history of parenchymal liver disease, contact with hepatitis or recent blood transfusion were excluded also, as were patients whose average daily intake of alcohol exceeded 3 units and those whose weight was greater than 120% of that expected for a person of the same age, sex and height [10]. Subjects were allocated, according to a previously prepared, randomized, sex-stratified list, to one of two groups to receive either an i.v. infusion of nicardipine or a comparable infusion of normal saline.

The infusion was designed to achieve a steady state plasma concentration of nicardipine approximately 120 ng ml^{-1} after 1 h of infusion, based on an approximate plasma clearance rate of nicardipine of 600 ml min^{-1} for a 70-kg subject and an elimination rate constant of 0.2 h^{-1} [11]. The contents of a syringe containing nicardipine 5 mg in normal saline 60 ml were infused from a syringe pump at a rate of 1 ml min^{-1} into a closed vial containing nicardipine 20 mg in 20 ml volume, via a fine-bore needle to encourage mixing within the vial. The infusion was led from the vial to the patient. This technique was described by Riddell and co-workers [12]. In the first 1 h of this treatment a patient allocated to receive nicardipine would have been given a combination of a steady infusion of nicardipine 5 mg and an exponentially decreasing infusion with a total of nicardipine 20 mg, 95% of which would have been administered in that time. Subsequently, an infusion was started of nicardipine 25 mg in normal saline 50 ml at 10 ml h^{-1} for a further 5 h.

The infusion was commenced 1 h before induction of anaesthesia. The electrocardiograph was monitored continuously and systemic arterial pressure measured for the duration of the infusion, which was discontinued if the systolic arterial pressure became less than 75% of the preinfusion value, or if tachycardia > 150 beat min^{-1} or disorders of cardiac rhythm became apparent.

Premedication comprised temazepam 20 mg by mouth 2 h before operation. Anaesthesia was induced with thiopentone 4–6 mg kg^{-1} and suxamethonium 1 mg kg^{-1} was administered to facilitate tracheal intubation if this was necessary. Anaesthesia was maintained with 66% nitrous oxide and halothane in oxygen. Ventilation was spontaneous in all patients. End-tidal concentrations of halothane (Penlon halothane meter) and carbon dioxide (Hewlett–Packard 47210A capnometer) were recorded every 5 min for the duration of anaesthesia. The carbon dioxide sensor was attached to the mount of the mask in non-intubated patients. Patients were withdrawn from the study if their end-tidal carbon dioxide partial pressure exceeded 8 kPa. Postoperative analgesia was provided by i.m. diamorphine, oral dihydrocodeine or soluble aspirin as necessary; metoclopramide was prescribed to relieve nausea.

The patient's age, height, weight, alcohol intake, the operation performed and the duration of anaesthesia were recorded, and end-tidal carbon dioxide and halothane concentrations were recorded for each 5-min period. The mean of the end-tidal concentrations of carbon dioxide and halothane was determined for each patient and a time-weighted halothane average calculated (mean end-tidal halothane concentration × duration of anaesthesia (min)). Blood was sampled before commencing the infusion, for GST and conventional liver function tests, full blood count and screening for the following autoantibodies: thyroid cytoplasm, gastric parietal cells, antinuclear factor, smooth muscle, mitochondria and antibrush border. Further samples for measurement of GST were taken 1, 3, 6 and 24 h after induction of anaesthesia. Plasma concentration of nicardipine was assessed at the end of the exponential infusion and 30 min and 1, 2, 3 and 6 h after induction. At 24 h a final sample of blood was taken for repeat blood chemistry and haematological screening.

Assay procedures

Concentrations of bilirubin, and activities of alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT) were measured using a Sequential Multiple Analysis with Computer System II (SMAC) (Technicon Instrument Corporation, Basingstoke, U.K.). The plasma concentration of GST B_1B_1 was measured by specific radioimmunoassay [13]. The reference range for GST B_1B_1 is 0.7–4.0 µg litre^{-1}. The interassay coefficient of variation for the GST radioimmunoassay was less than 10%, and the intraassay coefficient of variation was less than 5% over the range 2–40 µg litre^{-1}. Samples for nicardipine assay were separated by centrifugation and the resultant serum was stored at −20 °C until assay was performed by standard high pressure liquid chromatography [14]. Analysis of nicardipine-containing serum was performed

TABLE I. *Median (range) values of conventional liver function tests for 16 patients excluded from analysis because of abnormal values before operation, and median values of GST for these patients*

	Before op	After operation			
		1 h	3 h	6 h	24 h
Bilirubin (μg litre^{-1})	10 (6–15)	—	—	—	13 (6–26)
ALT (u. litre^{-1})	39 (20–108)	—	—	—	36 (20–85)
GGT (u. litre^{-1})	31 (9–159)	—	—	—	24 (6–151)
GST (μg litre^{-1})	5.9 (4.6–27.6)	5.0 (3.5–24.7)	6.4 (3.3–29.2)	5.0 (3.4–17.4)	3.6 (1.7–8.5)

by Syntex Pharmaceuticals Ltd, Palo Alto, California.

Statistical procedures

The demographic data, the duration of anaesthesia, mean end-tidal halothane and carbon dioxide concentration, and time-weighted halothane average for each group were compared using Student's *t* test. Changes in GST concentrations within each group were compared using the Friedman test. The GST changes from the preoperative values at 1, 3, 6 and 24 h following induction of anaesthesia in each group were compared by the Wilcoxon signed rank test. Differences in GST changes at these times between the two groups were examined by the Wilcoxon rank sum test. The relations between changes in GST concentration and duration of anaesthesia, end-tidal carbon dioxide concentration, and dose of opioid administered in 24 h were examined by Spearman's rank coefficient. This test was also used to investigate the correlation of GST changes and plasma nicardipine concentration for males and females separately.

RESULTS

Eighty patients were entered into the study: 42 received nicardipine (27 males, 15 females) and 38 received placebo (26 males, 12 females). The infusion was discontinued in 11 patients and they were excluded from subsequent analysis. Eight of these had received nicardipine and on each occasion the infusion was stopped because of hypotension. Three patients receiving normal saline also had the infusion discontinued, two because of tachycardia and one whose operation was cancelled for surgical reasons. Data were not analysed in 16 patients who were found to have abnormal liver function tests in the sample taken before operation (table I). All exhibited an increased GST and nine also had abnormal conventional liver function tests. In no patient did end-tidal carbon dioxide partial pressure exceed 8 kPa, and only four patients had values greater than 6 kPa.

The remaining 53 patients from whom data were analysed comprised 29 who received nicardipine (17 males, 12 females) and 24 who were given placebo (13 males, 11 females). Comparisons between the groups revealed no significant difference in age, height, weight, percent of expected weight and daily alcohol consumption (table II). Two patients in the study were taking regular oral medication: one was receiving temazepam and the other bendrofluazide. Both groups received similar doses of thiopentone at induction of anaesthesia, when three patients in the placebo group and two in the nicardipine group received suxamethonium to facilitate tracheal intubation. Mean end-tidal values of halothane and carbon dioxide concentrations did not differ significantly between groups. Patients receiving nicardipine had a significantly longer duration of anaesthesia than those receiving placebo ($P < 0.01$) and, as would be expected, their time-weighted halothane average was correspondingly greater ($P < 0.05$) (table II).

TABLE II. *Demographic data and anaesthetic characteristics (mean (SD))*

	Placebo	Nicardipine
Age (yr)	34 (12)	30 (8)
Height (cm)	171 (10)	174 (11)
Weight (kg)	68 (9)	71 (13)
Percent of expected wt	100 (12)	103 (12)
Alcohol (u day^{-1})	1.4 (0.8)	1.6 (1.1)
Thiopentone (mg)	414 (63)	428 (86)
Halothane concn (%)	1.1 (0.3)	1.0 (0.2)
$P_{E'_{CO_2}}$ (kPa)	4.9 (0.8)	5.1 (0.7)
Duration of anaesthesia (min)	39 (11)	54 (21)
Time-weighted halothane average	40.3 (13.7)	53.1 (21.5)

TABLE III. *Median values of GST* (*µg litre*$^{-1}$) (*interquartile range*) $*P < 0.05$, $**P < 0.01$ *compared with value before operation*

	Before op.	After operation 1 h	3 h	6 h	24 h
Placebo	2.2 (1.8–2.8)	2.1 (1.6–2.8)	2.7** (2.2–3.4)	2.8** (2.2–3.3)	2.0 (1.7–2.6)
Nicardipine	2.4 (1.7–2.8)	2.0 (1.7–2.9)	2.9** (2.3–4.2)	2.5* (2.1–3.6)	1.7* (1.4–2.4)

A significant increase in plasma GST concentration above basal values was noted 3 and 6 h following induction in each group and a significant reduction at 24 h in the group receiving nicardipine (table III). The distribution of changes in GST from the preoperative values is shown in figure 1. Nicardipine administration resulted in a greater increase in GST concentration 3 h after induction than did placebo ($P < 0.05$). This difference was almost entirely attributable to males receiving nicardipine, who showed a greater increase in GST value at 3 h ($P < 0.01$) than did females receiving nicardipine (fig. 2). The median plasma concentrations of nicardipine at each time of sampling are shown separately for males and females in table IV. Males receiving nicardipine had significantly lower plasma concentrations of nicardipine than females at the end of the exponential infusion and at 2 h after induction ($P < 0.05$, both times). The plasma concentration of nicardipine at these times was inversely related to the increase in GST at 3 h ($P < 0.01$ at the end of exponential infusion, $P < 0.05$ at 2 h after induction (fig. 3)). There was no correlation between the magnitude of change in GST at 3 and 6 h and duration of anaesthesia, mean end-tidal carbon dioxide concentration or administration of opioid after operation in either group.

The finding of positive autoantibody titres in seven patients (two to gastric parietal cells, two to

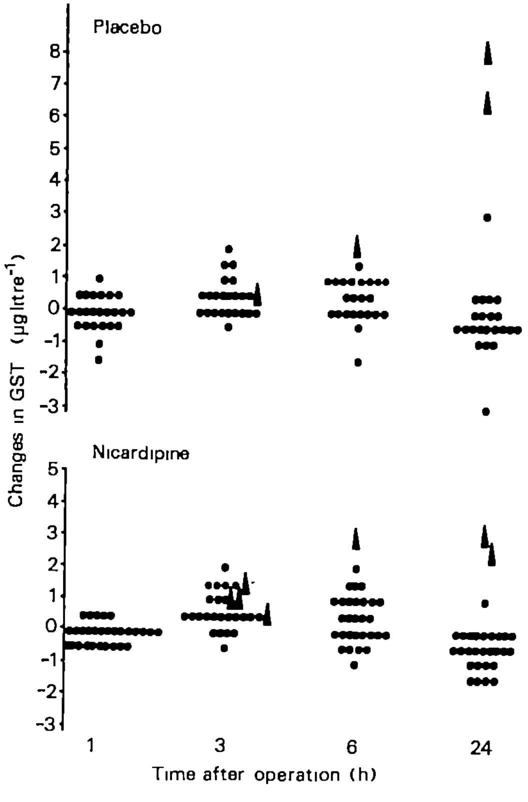

FIG. 1 Individual changes in plasma GST concentrations after operation, relative to the preoperative value, for the patients receiving placebo and nicardipine infusions Arrowheads = increase in GST that exceeded the upper limit of the reference range

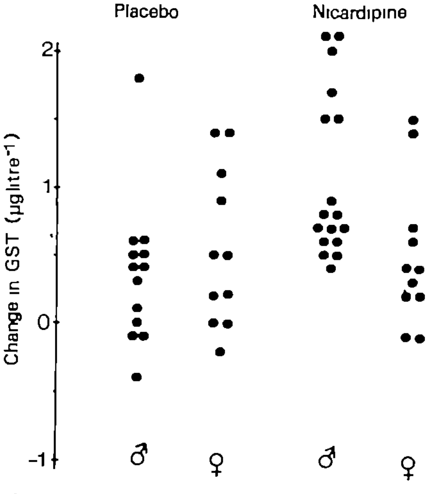

FIG 2 Individual changes in plasma GST concentrations, relative to the preoperative value, 3 h after operation, showing male and female subjects separately

TABLE IV. *Plasma nicardipine concentrations* (*ng ml*$^{-1}$) (*median* (*range*)) * $P < 0.05$ *between sexes*

	End of exponential infusion	Time after induction				
		30 min	1 h	2 h	3 h	6 h
Males	115.2 (61.0–149.5)	90.8 (67.4–159.3)	90.3 (72.1–117.3)	79.7 (64.9–118.6)	80.6 (63.2–128.3)	35.5 (20.2–58.5)
	*			*		
Females	149.8 (87.5–196.0)	107.7 (52.5–158.2)	99.4 (77.0–166.6)	105.4 (75.7–149.2)	103.8 (59.5–139.6)	34.8 (18.8–54.0)

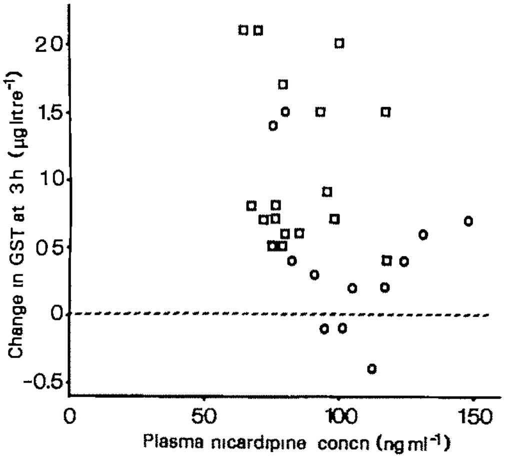

FIG. 3 Relationship between the plasma concentration of nicardipine achieved 2 h after induction of anaesthesia, and the change in GST that occurred at 3 h after induction of anaesthesia. □ = Male patients; ○ = female patients. There is a negative linear correlation ($r = -0.43$, $P < 0.05$) for the patients taken together

antinuclear factor, and one each to thyroid cytoplasm, smooth muscle and antibrush border) could not be related to an unusual GST response. The concentrations of bilirubin and activities of ALT and GGT at 24 h after induction were not significantly different compared with the values before operation (table V).

TABLE V. *Mean* (*SD*) *values of conventional liver function tests*

	Bilirubin (μg litre^{-1})	ALT (u. litre^{-1})	GGT (u. litre^{-1})
Placebo			
Before op.	11 (4)	16 (10)	14 (14)
After op.	11 (4)	14 (8)	12 (13)
Nicardipine			
Before op.	14 (8)	17 (8)	14 (7)
After op	16 (12)	13 (8)	13 (7)

DISCUSSION

The underlying mechanisms of "halothane hepatitis" remain poorly understood. Hypersensitivity [15, 16], toxic products of metabolism [17–19] particularly non-oxidative metabolism [20], regional hepatic hypoxia [21, 22] and a familial susceptibility factor [23] have all been implicated as contributing factors. Females are reported to be at greater risk than males of developing hepatic damage following halothane anaesthesia [24, 25], although the sex distribution of patients exposed to halothane anaesthesia is not necessarily equal. It was for this reason that we investigated independently the influence of nicardipine infusion on GST release in the two sexes.

It has been suggested that an increase in intracellular calcium acts as the final common event in irreversible cell damage [4]. Such an increase occurs secondary to disruption of the mechanisms that maintain intracellular calcium homeostasis. Recently, it has been postulated that the difference in toxicity between halothane and isoflurane might result from a different ability of anaesthetics to disrupt intracellular calcium homeostasis [5]. The administration of a calcium channel blocker before the initiation of cell injury may therefore prevent a large secondary influx of calcium into the cell and limit the severity of cellular damage. Indeed, studies in the rat suggest that this is the case [7, 8]. We undertook this study to investigate the degree to which calcium channel blockade could reduce liver dysfunction following halothane anaesthesia.

We have confirmed that transient GST release occurs following anaesthesia with halothane in man, as has been demonstrated previously [2, 3]. Although the changes in median concentrations of GST were small, some individual increases were sufficient to increase the plasma concentration of GST above the upper limit of the reference range.

This finding parallels those of earlier studies in which the administration of isoflurane did not result in an increase in plasma concentration of GST [2, 3]. We have also shown that nicardipine is associated with a greater release of GST after operation than is placebo. This difference resulted from an exaggerated GST response in males, but not females, receiving nicardipine. Females had a significantly greater plasma concentration of nicardipine at the end of the exponential infusion and at 2 h after induction than males, and this was related to a lesser increase in GST at 3 h. The larger increase in GST at 3 h in males receiving nicardipine may reflect the combined effects of halothane and nicardipine causing a greater reduction in hepatic perfusion than halothane alone. The greater plasma concentration achieved in females perhaps conferred a degree of hepatoprotection against this combined effect, but possibly were still insufficient to prevent release of GST. Although plasma concentrations of nicardipine throughout the infusion were compatible with those required to give a clinically relevant effect [26] and haemodynamic effects were apparent throughout the infusion (increased heart rate and reduced diastolic arterial pressure), it may be that even greater plasma concentrations are required for hepatoprotection following halothane anaesthesia. Such concentrations may, however, cause undesirable cardiovascular side effects. We were unable demonstrate that nicardipine in the dose administered prevented this type of liver dysfunction.

The finding that nicardipine conferred no hepatoprotection is at variance with animal studies. However, the dose of nicardipine administered to rats [8] was 25 to 50 times greater than the total dose given to patients in the present study. As we have suggested, larger doses of nicardipine given to man might also have the same protective effect. In the same animal studies the agents used to induce hepatic injury were carbon tetrachloride and d-galactosamine. The pattern of hepatotoxicity caused by these agents may not resemble the centrilobular necrosis seen with halothane, so a comparison of the protective effect of nicardipine for different hepatotoxins may not necessarily be appropriate.

In animal studies the severity of hepatic damage caused by halothane is related to halothane concentration, but this has not been demonstrated in humans. Despite the random allocation design of this study, the patients receiving nicardipine had on average a longer duration of anaesthesia and consequently a greater time-weighted halothane average than patients given placebo. This raises the possibility that a greater hepatic insult was imposed in the patients receiving nicardipine. However, no correlation was detected between duration of anaesthesia and magnitude of GST increase, a finding in aggreement with those of Allan [2] and Hussey [3], suggesting that this difference between the groups is unlikely to have influenced our findings.

As in previous studies investigating GST release following halothane anaesthesia, some patients exhibited a large secondary increase in plasma GST activity 24 h after induction (fig. 1). These patients were distributed equally between the two groups and nicardipine seemed of no benefit in preventing this less frequent increase, although many more patients would require study to be certain of this.

In compliance with the study programme, patients with abnormal liver function tests before operation were excluded from analysis. It could be argued that we thus introduced a degree of bias into the results by selecting "normal" patients. However, an examination of GST concentrations after operation in the 16 patients so excluded revealed a pattern of GST change similar to that seen in those patients who were entered into analysis.

GST is a sensitive marker allowing investigation of liver dysfunction following use of volatile anaesthetic agents in man. Further investigations are required to elucidate the mechanisms involved.

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EFFECT OF DILTIAZEM ON PORCINE MALIGNANT HYPERPYREXIA INDUCED BY SUXAMETHONIUM AND HALOTHANE

P. S. FOSTER, K. C. HOPKINSON AND M. A. DENBOROUGH

SUMMARY

We have studied the ability of the calcium channel antagonist diltiazem to inhibit and reverse the porcine malignant hyperpyrexia (MH) syndrome. Pretreatment with diltiazem modified an MH response. Treatment with diltiazem was partially effective against a mild (or early) MH response. Diltiazem should not be considered to be an effective therapeutic agent for MH and should not displace the use of dantrolene.

Porcine MH may be induced by suxamethonium and halothane [1,2]. In the presence of a precipitating agent, the clinical features of the porcine MH syndrome are similar to those described in man. Essentially, MH in swine is characterized by a rapid and sustained increase in core body temperature and muscle rigidity. Biochemical changes such as metabolic acidosis and increased arterial carbon dioxide tensions precede the development of these features [1]. Increases in serum electrolytes and creatine phosphokinase (CPK) concentrations are detected also during and after the syndrome [1,3].

An increased concentration of Ca^{2+} in the myoplasm of skeletal muscle is considered to be the major factor in the development of MH [3,4]. Successful management requires early diagnosis, immediate cessation of anaesthesia, correction of metabolic acidosis by i.v. administration of sodium bicarbonate and prompt i.v. administration of the drug dantrolene sodium [3]. Dantrolene acts to decrease myoplasmic concentrations of Ca^{2+} by suppressing excitation–contraction coupling. One of the rationales for the original use of dantrolene in the treatment of MH was based on the demonstration that the skeletal myoneural blocking drug could prevent and antagonize the contracture responses to the diagnostic agents halothane and caffeine in isolated muscle fibres [5].

The calcium channel antagonist diltiazem also has been shown to inhibit and antagonize the drug-induced hypercontractility of isolated MHS human and porcine muscle preparations [6–8]. It seems that diltiazem acts to inhibit Ca^{2+} fluxes associated with the transverse tubular membrane in skeletal muscle [8,9].

This study has investigated the therapeutic value of diltiazem in inhibiting and antagonizing the porcine MH syndrome.

MATERIALS AND METHODS

Six MH-susceptible (MHS) and four control pigs (body weights 25–47 kg, both sexes) were selected from mixed litters. All were premedicated by i.m. injection of stresnil (4-fluor-4(4-(2-pyridyl)-1-piperazinyl)-butyrophenone) 1.5–2 mg kg^{-1}. Tracheal intubation was performed after anaesthesia was induced with thiopentone 3–4 mg kg^{-1}. Anaesthesia was maintained with nitrous oxide in oxygen supplemented with thiopentone. Muscle tissue for the diagnosis of susceptibility was removed and anaesthesia maintained subsequently with 66% nitrous oxide in oxygen. Susceptibility to MH was identified by using the established isolated contracture test [10]. Physiological variables were recorded every 1 min for approximately 15 min and venous blood was taken for biochemical analysis. Suxa-

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methonium and halothane were administered in the presence (inhibition experiment) or absence (antagonism experiment) of diltiazem.

Administration of diltiazem

Diltiazem (Marion Laboratories) was dissolved in sterile water (Abbot Laboratories) to a final concentration of 1 mg ml^{-1} and administered i.v. through a catheter placed in the ear. The rate of administration varied but did not exceed 1 mg kg^{-1} min^{-1}. This prevented dramatic and sustained decreases in arterial pressure.

Inhibition experiments

Increasing doses of diltiazem were administered i.v. to a total dose of 2, 5 or 10 mg kg^{-1} (one, one and four pigs, respectively). After physiological variables had stabilized, suxamethonium was administered i.v. (ear vein) in four doses (to reduce fasciculations) to a total dose of 2 mg kg^{-1}. If required, the lungs were ventilated manually at a constant rate until ventilatory function returned. After the administration of the neuromuscular blocker, nitrous oxide was discontinued and anaesthesia with 1 % halothane in oxygen initiated. Halothane anaesthesia was maintained for approximately 90 min. Physiological variables were monitored every 1 min for the duration of the challenge. Blood for biochemical analyses was taken and anaesthesia ceased.

Antagonism experiments

MHS pigs were allowed to recover for no less than 2 weeks before being challenged again in the absence of diltiazem. After vital signs had stabilized under nitrous oxide–oxygen anaesthesia, suxamethonium was administered in four doses to a total concentration of 2 mg kg^{-1} and 1 % halothane administered. After the initiation of an MH syndrome, halothane was discontinued and increasing doses of diltiazem were administered i.v. to a total concentration of 7–10 mg kg^{-1} in five pigs and 2 mg kg^{-1} in one other. Sodium bicarbonate was also administered i.v. and anaesthesia was maintained with 66 % nitrous oxide in oxygen. Blood samples for biochemical analysis were taken: (1) immediately before the administration of suxamethonium and halothane, (2) when the MH syndrome was established and (3) after administration of diltiazem. Vital signs were monitored every 1 min throughout the challenge.

The same procedure was followed with control pigs, blood being taken for biochemical analysis under nitrous oxide–oxygen anaesthesia and at two periods during halothane anaesthesia. Halothane anaesthesia was maintained for 90 min.

Criteria for establishing the initiation of an MH episode

In this study, an MH episode was considered to have occurred when body temperature increased by at least 1 °C, a clinical score of at least 3 was obtained for extensor rigidity, and tachycardia and a decreasing arterial pressure were observed. Often, abnormal patterns also were observed on the electrocardiogram (ECG). While metabolic changes such as increased Pa_{CO_2} and lactate precede the development of muscular rigidity and hyperpyrexia during an MH crisis, it was not possible to monitor these continuously throughout the duration of the challenge. The syndrome was therefore characterized primarily by muscular rigidity and increased body temperature. The development of these later features of MH was considered sufficient to render any observed response to diltiazem unequivocal.

An increase in rectal temperature of 1 °C was considered sufficient to indicate an MH reaction, as increased body temperature is not only a late feature of an MH episode, but occurs also against a tendency to hypothermia under halothane anaesthesia. Furthermore, death has occurred at rectal temperatures as low as 40 °C in MH pigs [11].

In two pigs which had been used for inhibition and antagonism experiments, MH was induced again under identical conditions. Halothane anaesthesia was discontinued and sodium bicarbonate administered at stages in the reaction which were similar to those of previous antagonism experiments. These experiments were conducted with a view to establishing that withdrawal of the triggering agent would not prevent the development of the hyperpyrexic response.

Physiological measurements

Arterial pressure was monitored via a femoral arterial catheter connected to a pressure transducer (Bentley) coupled to a cardiac monitor (Telectronics HSG). Patency of the catheter was maintained by a constant infusion of (approximately 10 ml h^{-1}) heparinized saline solution 1000 units $litre^{-1}$. Electrodes were also placed for the monitoring of heart rate and ECG. Rectal temperature was measured using a mercury-in-

TABLE I. *Effect of diltiazem in malignant hyperpyrexia pigs in the presence of suxamethonium and halothane: physiological variables (mean or mean (SEM)) from six MH-susceptible swine. Swine were premedicated with diltiazem before administration of suxamethonium and halothane. After recovery of at least 2 weeks, MH episodes were precipitated by suxamethonium and halothane and the effect of diltiazem observed*

Anaesthetic conditions	Temperature (°C)	Extensor rigidity (Clinical score)	Heart rate (beat min^{-1})	Arterial pressure (SAP/DAP) (mm Hg)
Inhibition of MH				
Nitrous oxide–oxygen	36.0	0	80.3 (2.8)	99/58 (2.5/2.3)
Diltiazem 2–10 mg kg^{-1}, suxamethonium 2 mg kg^{-1} and halothane	35.0	0	97 (5.6)	93/48 (2.9/2.6)
Antagonism of MH				
Nitrous oxide–oxygen	37.2	0	77 (1.94)	105/54 (2.6/2.5)
Suxamethonium 2 mg kg^{-1} and 1% halothane (precipitation of MH)	38.3	3–4	163 (21.52)	74/42 (5.9/3.7)
After diltiazem 2–10 mg kg^{-1}, halothane off, N_2O/O_2 on, $NaHCO_3$ i.v.	37.2	0	114 (11.97)	86/46 (3.4/2.2)

glass thermometer. Muscular rigidity of the front extensor was estimated and given a clinical score: 0 = flaccid extensor; 1 = initiation of rigidity; 2 = mild rigidity; 3 = pronounced rigidity of extensor; 4 = severe rigidity, difficulty in bending extensor; 5 = rigor, unable to bend extensor.

Biochemical measurements

Arterial blood samples were taken and analysed for pH, Pa_{CO_2}, Pa_{O_2}, potassium, inorganic phosphate, calcium, lactate and CPK. Blood-gas analysis was conducted within 30 min of sampling. All biochemical measurements were conducted by the Department of Clinical Biochemistry at Royal Canberra Hospital.

RESULTS

Inhibition experiments

Pretreatment of MHS pigs with diltiazem modified the induction of the MH syndrome by suxamethonium 2 mg kg^{-1} and 1% halothane (tables I, II) over a 90-min period. In the absence of diltiazem, all reactor pigs developed the syndrome within 15–30 min (see antagonism experiments). In the presence of diltiazem, extensor muscles remained flaccid and body temperature decreased by approximately 1 °C. Arterial pressure decreased following administration of diltiazem and recovered within 5–10 min (results not shown). Heart rate did not exceed 100 beat min^{-1}. Blood pH and base excess values decreased slightly, but not to the same degree as observed during an MH episode (table II). Similar observations were made during anaesthesia in control swine (table III). Furthermore, in MHS pigs treated with diltiazem, plasma lactate concentration did not increase, and blood-gas analysis indicated that Pa_{CO_2} and Pa_{O_2} did not change markedly. Plasma concentrations of calcium, potassium and inorganic phosphate also remained essentially unchanged. CPK concentration did increase in pretreated animals during anaesthesia, by 638 u. $litre^{-1}$ (table II). However, this increase was substantially less than that in untreated pigs (2112 u. $litre^{-1}$) (table II) and was probably a result of muscular fasciculations induced by suxamethonium.

Antagonism experiments

Treatment with diltiazem was partially effective against a mild (or early) MH response. Exposure of MHS pigs to suxamethonium 2 mg kg^{-1} and 1% halothane in the absence of diltiazem resulted in the development of the MH syndrome (tables I and II). Pigs developed pronounced muscular rigidity (clinical score of 3–4), followed by an increase in rectal temperature. Heart rate doubled

TABLE II. *Effect of diltiazem in malignant hyperpyrexia pigs in the presence of suxamethonium and halothane: biochemical variables (mean (SEM)) from six MH-susceptible swine. Swine were premedicated with diltiazem before administration of suxamethonium and halothane After recovery of at least 2 weeks, MH episodes were precipitated by suxamethonium and halothane and the effect of diltiazem observed*

Anaesthetic conditions	CPK (u. litre^{-1})	pH	Pa_{CO_2} (kPa)	Pa_{O_2} (kPa)	Base excess (mmol litre^{-1})	Lactate (mmol litre^{-1})	K (mmol litre^{-1})	PO_4 (mmol litre^{-1})	Ca (mmol litre^{-1})
Inhibition of MH									
Nitrous oxide–oxygen	1410 (250)	7.41 (0.01)	5 8 (0.3)	40.7 (2.9)	3.12 (0.34)	2.8 (0.51)	3 1 (0.21)	2.3 (0.51)	2.3 (0.25)
Diltiazem 2–10 mg kg^{-1}, suxamethonium 2 mg kg^{-1}, halothane	2048 (287)	7.36 (0.03)	6.0 (0.3)	33 5 (4.0)	1.9 (0.44)	1.9 (0.63)	3.7 (0.31)	2.4 (0.21)	2.4 (0.32)
Antagonism of MH									
Nitrous oxide–oxygen	1670 (299)	7 42 (0.01)	6.1 (0.3)	45.6 (3.5)	5.03 (1.24)	3.8 (0.51)	3 3 (0.12)	2.5 (0.11)	2 4 (0.06)
Suxamethonium 2 mg kg^{-1}, 1 % halothane (precipitation of MH)	3515 (186)	7.26 (0.01)	8.5 (0.4)	28.5 (2.5)	0.62 (0.59)	6.9 (0.41)	4.5 (0.55)	3.0 (0.16)	2.3 (0.04)
After diltiazem 2–10 mg kg^{-1}, halothane off, N_2O/O_2 on, $NaHCO_3$ i.v.	3782 (577)	7.44 (0.02)	5.4 (0.4)	34.0 (5.3)	6.3 (0.46)	—	4.8 (0 46)	3.1 (0.23)	2.3 (0.09)

and blood-gas analysis showed an increase in Pa_{CO_2} tensions of 2.31 kPa and a decrease in Pa_{O_2}. Plasma lactate concentration increased from 3.8 to 6.9 mmol litre^{-1} while blood pH and base excess decreased by 0.16 units and 4.4 mmol litre^{-1}, respectively, consistent with metabolic acidosis (table II). Plasma potassium and inorganic phosphate concentrations were increased during and after the challenge, while calcium concentration remained virtually unchanged. CPK concentration also increased, approximately two-fold (table II). In three of the

TABLE III. *Effect of suxamethonium and halothane on the physiological and biochemical variables of four control swine (mean or mean (SEM))*

	Anaesthetic conditions		
	N_2O/O_2	Suxamethonium + halothane (after 30 min anaesthesia)	Suxamethonium + halothane (after 90 min anaesthesia)
Temp. (°C)	36.3	35.7	35 6
Rigidity (clinical score)	0	0	0
CPK (u. litre^{-1})	953.5 (64.76)	1059 (20)	1119 (27)
Heart rate (beat min^{-1})	86 (3.17)	90 (4.4)	95 (6.25)
Arterial pressure (SAP/DAP) (mm Hg)	112/65 (5.7/5.7)	105/65 (5.2/5.7)	103/61 (4.7/5.0)
pH	7.37 (0.03)	7.4 (0.03)	7.35 (0.02)
Pa_{CO_2} (kPa)	6.5 (0.5)	6.3 (0.6)	7.1 (0.4)
Pa_{O_2} (kPa)	39.8 (7 7)	55.5 (5.7)	55.6 (7.5)
BE (mmol litre^{-1})	2.02 (0 42)	3.38 (0.83)	2.84 (0 85)
Lactate (mmol litre^{-1})	3.50 (0.2)	2.67 (0.21)	2.84 (0.33)
K (mmol litre^{-1})	3.1 (0.11)	3.6 (0.24)	3.4 (0.12)
PO_4 (mmol litre^{-1})	2.0 (0.19)	1.9 (0.17)	2.1 (0.09)
Ca (mmol litre^{-1})	2 3 (0 02)	2.1 (0.08)	2.1 (0.05)

six challenged pigs, blotchy cyanosis of the skin was also observed.

When the clinical features of MH had been identified, with muscular rigidity and an increase in body temperature of at least 1 °C, diltiazem 2–10 mg kg^{-1} was administered i.v. Diltiazem caused a rapid decrease in both systolic and diastolic arterial pressures (results not shown). However, administration of small doses of diltiazem with careful monitoring of arterial pressure prevented sustained hypotension. Arterial pressure recovered to pre-administration values within 5–10 min (allowing further administration if required). The administration of diltiazem caused a rapid loss of extensor rigidity, followed by a progressive decrease in rectal temperature. Heart rate decreased, while arterial pressure remained low in the presence of diltiazem. Blood pH, base excess and Pa_{CO_2} returned to values approaching those before the challenge. Pa_{O_2} also increased (table II). A total concentration of diltiazem 7–10 mg kg^{-1} was required to antagonize the MH syndrome in five pigs and 2 mg kg^{-1} was needed in another. The only ancillary treatment pigs received was the administration of sodium bicarbonate; active cooling of one pig was required after body temperature had increased above 40 °C. All pigs survived.

In two MHS swine which had previously been included in inhibition and antagonism experiments, MH was induced under identical conditions. Halothane anaesthesia was discontinued and sodium bicarbonate administered at stages in the reaction which were similar to previous antagonism experiments. Both pigs developed fulminant MH and died. This suggests that metabolism had been stimulated sufficiently and withdrawal of the triggering agent did not prevent the development of the hyperpyrexic response.

Suxamethonium and halothane anaesthesia in control pigs

Temperature decreased by approximately 1 °C and extensors remained flaccid during suxamethonium 2 mg kg^{-1} and 1 % halothane-induced anaesthesia in control swine (table III). Physiological and biochemical features remained essentially constant.

DISCUSSION

The calcium channel antagonist diltiazem modified and partially antagonized a mild (or early) MH response. In the absence of diltiazem, MH-susceptible pigs developed the characteristic clinical features of MH. These included hyperpyrexia, muscular rigidity, metabolic acidosis, increased plasma potassium, inorganic phosphate and CPK concentrations and increased Pa_{CO_2}. Tachycardia, arrhythmias (results not shown) and hypotension were also observed.

Blood-gas analysis in unpretreated swine was consistent with the early expression of the MH syndrome. In this study, all pigs underwent continuous or intermittent ventilation at a constant rate. Alterations in blood-gas values occurred in the absence of any obvious respiratory cause (eg. underventilation) and reflected metabolic acidosis and increased carbon dioxide production. A rapid decrease in base excess corresponding to the increase in Pa_{CO_2} was also observed. Furthermore, despite relatively high arterial Pa_{O_2} (> 27 kPa) at all times, lactate production reflecting anaerobic glycolysis was always observed during halothane anaesthesia in the absence of diltiazem in MH pigs. By comparison, Pa_{CO_2}, Pa_{O_2}, pH and base excess measurements remained essentially constant during halothane anaesthesia in control and diltiazem-pretreated MH pigs.

When MHS pigs were pretreated with diltiazem, suxamethonium and halothane did not trigger the MH syndrome. Skeletal muscle metabolism was not accelerated, and plasma lactate and arterial pH and blood-gas values remained essentially unchanged. Subsequently, extensors remained flaccid and cardiac dysfunction and increased plasma concentrations of inorganic phosphate and potassium were not observed. Also, rectal temperature decreased over the duration of the challenge. Plasma CPK concentrations increased, but not to the same degree as observed in unpretreated MHS pigs. This increase probably reflected increased muscular activity, observed as fasciculation after the administration of suxamethonium, as CPK concentrations increased also in control swine after the administration of suxamethonium. The clinical features of halothane anaesthesia in pretreated MHS pigs were essentially the same as those observed in control swine.

Furthermore, two MHS pigs in which MH was initiated by halothane (but which did not receive diltiazem), developed fulminant MH and died. This suggests that metabolism had been stimulated sufficiently and withdrawal of halothane did not prevent the development of the MH response. Similar observations have been made by other investigators who have shown that, when metabolism has been stimulated sufficiently, the MH syndrome can continue unabated with further increases in temperature in the absence of the triggering agent [1, 12, 13].

Pharmacological experiments indicate that diltiazem may modify Ca^{2+} fluxes at the level of the T-tubule membrane [8]. Ca^{2+} entering the muscle via T-tubules may therefore be important in the aetiology of the MH syndrome. Diltiazem not only acts on skeletal muscle, but also has well known cardiovascular effects [14]. Diltiazem prevents arrhythmias and protects the heart from ischaemia, effects which would be beneficial during an MH episode. Although diltiazem causes hypotension, this was not an adverse effect in this study during MH. The release of catecholamines from the adrenal medulla is a Ca^{2+}-dependent process [15]. The increased concentration of circulating catecholamines observed during an MH episode [12] may also be mediated by Ca^{2+} [3]. Diltiazem may also inhibit this Ca^{2+}-dependent process and attenuate cardiovascular changes [16].

In common with dantrolene, diltiazem modifies the onset of MH and the further expression of an initiated MH syndrome. However, diltiazem is not as effective as dantrolene, and should not displace this drug in the treatment of MH.

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EFFECT OF DILTIAZEM AND DANTROLENE ON THE CONTRACTILITY OF ISOLATED MALIGNANT HYPERPYREXIA-SUSCEPTIBLE PORCINE SKELETAL MUSCLE

P. S. FOSTER AND M. A. DENBOROUGH

SUMMARY

Diltiazem inhibited and antagonized the abnormal contractures induced by halothane, caffeine and potassium chloride in isolated skeletal muscle from pigs susceptible to malignant hyperpyrexia (MHS). Contractile responses to caffeine and electrical stimulation also were suppressed by diltiazem in control tissue. Similar effects were obtained in the presence of dantrolene In both MHS and control preparations, diltiazem antagonized caffeine-induced contractures in the presence of maximal effective concentrations of dantrolene, and the converse was true also In MHS and control preparations detubulated by glycerol, diltiazem did not inhibit or antagonize caffeine-induced contractures while dantrolene did. Diltiazem seems to modify contractile responses at the level of the transverse tubule membrane by inhibiting the inward flow of extracellular Ca^{2+}, while dantrolene inhibits Ca^{2+} release directly from the sarcoplasmic reticulum Ca^{2+} influx through transverse tubules may be important in the aetiology of the MH syndrome

The clinical features of malignant hyperpyrexia (MH) and the observed hypercontractility of isolated MH-susceptible (MHS) skeletal muscle fibres to certain chemical stimuli indicate a dysfunction in the processes which regulate myoplasmic Ca^{2+} concentration [1]. While the precise site of the lesion which predisposes to the abnormally high Ca^{2+} concentration is unknown, events of excitation–contraction coupling and Ca^{2+} transport by the sarcoplasmic reticulum (SR) have been implicated [2,3].

In skeletal muscle, voltage-dependent Ca^{2+} currents flow almost exclusively across the transverse tubular (T-tubular) membrane and are blocked by calcium channel antagonists [4]. Calcium channel antagonist receptors are localized preferentially at the T-tubular membrane, consistent with their association with calcium channels [5]. While the role of Ca^{2+} inflow through these Ca^{2+} channels during excitation–contraction coupling is not fully understood, it may play a functional role in the regulation of intracellular Ca^{2+} [6]. Dantrolene, the drug of choice in the treatment of MH, inhibits and antagonizes the abnormal contractile response of isolated MHS muscle [7]. The skeletal neuromuscular blocker acts primarily to decrease myoplasmic Ca^{2+} concentration by suppressing excitation–contraction coupling at the level of the triadic junction [8,9]. Calcium channel antagonists may therefore be able specifically to modify events of excitation–contraction coupling at the level of the T-tubular membrane and inhibit the MH response.

Preliminary investigations have shown that the calcium channel antagonist, diltiazem, inhibits the hypercontractility of MHS muscle to halothane [10,11]. We have investigated further the effect of diltiazem on the hypercontractility of MHS muscle induced by the diagnostic agents halothane, caffeine and potassium chloride. A comparative study with dantrolene was also conducted. The aims of these investigations were to establish if diltiazem is effective in regulating

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the abnormal Ca^{2+} fluxes in MHS muscle and to define further the site of the muscle abnormality.

MATERIALS AND METHODS

Ten pigs susceptible to MH and six control pigs were premedicated with stresnil (4-fluor-4(4-(2-pyridyl)-1-piperazinyl)-butyrophenone) 1.5–2 mg kg^{-1} i.m. Anaesthesia was induced with thiopentone 6–8 mg kg^{-1} i.v. and maintained with 66 % nitrous oxide in oxygen. During anaesthesia, gracilis muscle strips (4 × 1 × 0.5 cm) were clamped under tension and immediately removed into Ringer solution maintained at 37 °C, pH 7.4, and aerated continuously with 5 % carbon dioxide in oxygen. Bundles of muscle fibres (2 mm diameter, 2.5 cm long) were mounted vertically under 1.5 g of tension in organ bath chambers and bathed in Ringer solution maintained under the above conditions. Changes in isometric force were measured with a Watson Victor force displacement transducer coupled to a preamplifier (San-EI 6M51) and a chart recorder (Perkin–Elmer 56). Susceptibility to MH was identified using the established isolated contracture test [12]. Halothane 3 %, caffeine 2 mmol $litre^{-1}$ and potassium chloride 80 mmol $litre^{-1}$ induced hypercontractility in MHS muscle.

In experiments to determine the effects of diltiazem or dantrolene on contractures, muscle strips were equilibrated with the appropriate drug for 15–20 min. One concentration–effect curve was constructed for each muscle strip, by the addition of cumulative concentrations of caffeine to the bathing medium. In some experiments contractures were induced first and the effect of diltiazem or dantrolene was investigated subsequently. Some preparations were detubulated in addition, by immersing muscle strips under tension for 2 h in glycerol Ringer solution 400 mmol $litre^{-1}$ [13]. Preparations were washed repeatedly in normal Ringer solution (10 min) and stimulated electrically (30 V, 1 ms duration) until the twitch response was abolished. Concentration–effect responses to caffeine were constructed under the required conditions.

Halothane (thymol-free, ICI, Australia) was added to the bathing medium by passing 5 % carbon dioxide in oxygen at a constant rate of flow through a Dragewick vaporizer. Potassium chloride was added to the organ bath at a single concentration. Ringer solution was used as the bathing medium in all experiments. This contained (mmol $litre^{-1}$): NaCl 121; KCl 5.4; $NaHCO_3$ 15; NaH_2PO_4 1.2; $MgSo_4$ 1.2; $CaCl_2$ 2.5 and D-glucose 11.5.

Results are expressed as mean (SEM) tension (g). Significant differences in mean values were determined using Student's non-paired t test.

RESULTS

Identification of MHS and control muscle

MHS muscle preparations displayed the characteristic hypercontractility to 3 % halothane (0.93 (0.07) g, $n = 103$), caffeine 2 mmol $litre^{-1}$ (0.40 (0.03) g, $n = 120$) and potassium chloride 80 mmol $litre^{-1}$ (1.08 (0.11) g, $n = 78$). All contractures were significantly greater ($P < 0.001$) than in control preparations (halothane 0.09 (0.03) g, $n = 91$; caffeine 0.03 (0.01) g, $n = 89$; potassium chloride 0.14 (0.09) g, $n = 51$).

Effect of diltiazem and dantrolene on twitch response

Twitch responses were obtained in both MHS ($n = 6$) (fig. 1) and control ($n = 6$) isolated muscle preparations and were constant or decreased by only 10 % over a 2-h period. Diltiazem 80 µmol $litre^{-1}$ abolished the twitch response in MHS ($n = 5$) and control ($n = 5$) preparations in less than 2 h. Dantrolene 6 µmol $litre^{-1}$ reduced twitch height in both MHS ($n = 5$) and control

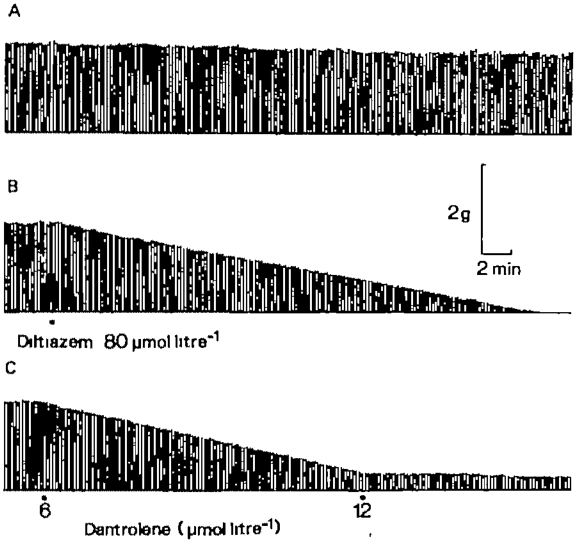

FIG. 1. Representative tracings of twitch responses (tension (g)) from isolated malignant hyperpyrexic susceptible (MHS) muscle in the absence (A) and presence of diltiazem (B) and dantrolene (C).

TABLE I. *Effect of diltiazem on contractures (mean (SEM) g) induced by halothane and potassium chloride in malignant hyperpyrexia susceptible muscle.* n = *No. observations.* * *Significant decrease* ($P < 0.001$)

	No additions	Diltiazem 80 µmol litre^{-1}	Dantrolene 6 µmol litre^{-1}
Halothane 3%	0.93 (0.07) $n = 103$	0.05 (0.02)* $n = 10$	0.09 (0.08)* $n = 11$
KCl 80 mmol litre^{-1}	1.08 (0.11) $n = 78$	0.05 (0.02)* $n = 20$	0.01 (0.01)* $n = 8$

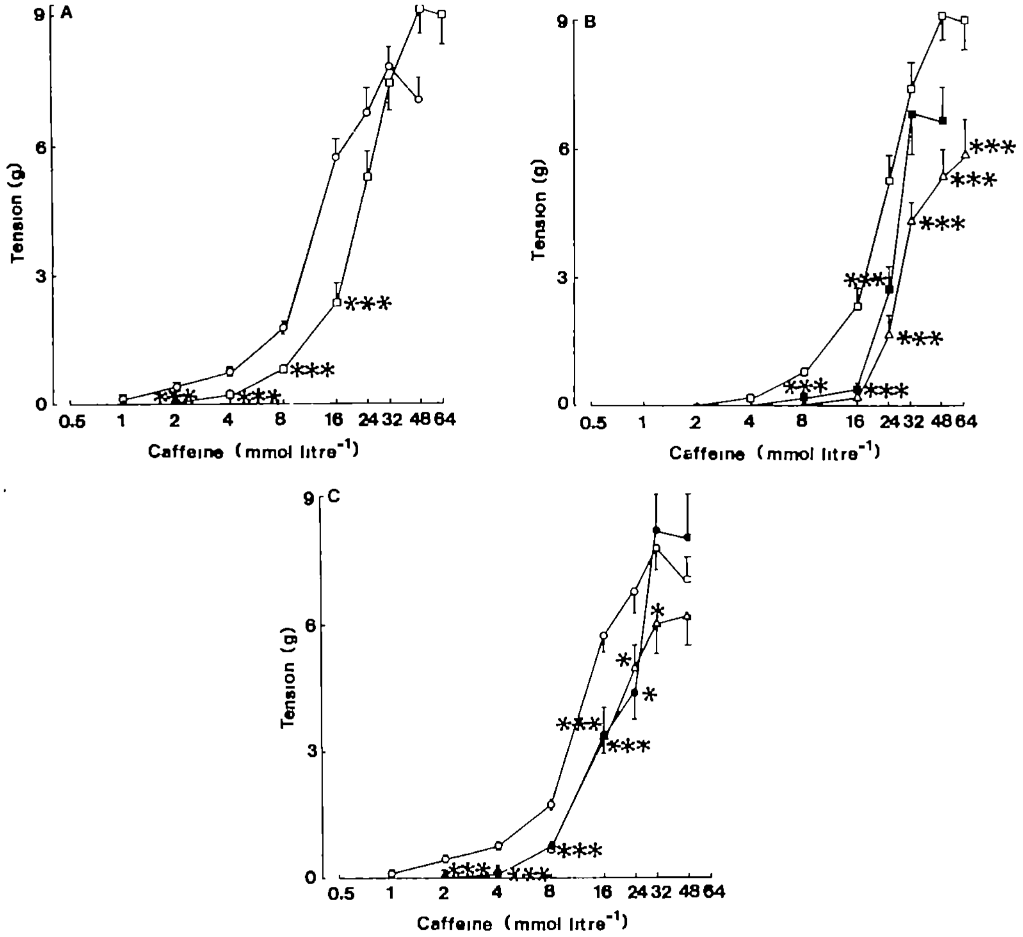

FIG. 2 Cumulative concentration–effect curves (mean (SEM)) to caffeine in isolated MHS (○) and control (□) porcine skeletal muscle preparations. A: Caffeine-induced responses in MHS and control preparations. B: Effect of diltiazem 80 µmol litre^{-1} (■) and dantrolene 6 µmol litre^{-1} (△) on caffeine-induced contractures in control muscle. C: Effect of diltiazem 80 µmol litre^{-1} (●) and dantrolene 6 µmol litre^{-1} (△) on caffeine-induced contractures in MHS muscle. Number of observations. 24–120 (untreated MHS and control preparations); 11–16 (preparations pretreated with diltiazem or dantrolene). Significant differences: *$P < 0.05$; ***$P < 0.001$.

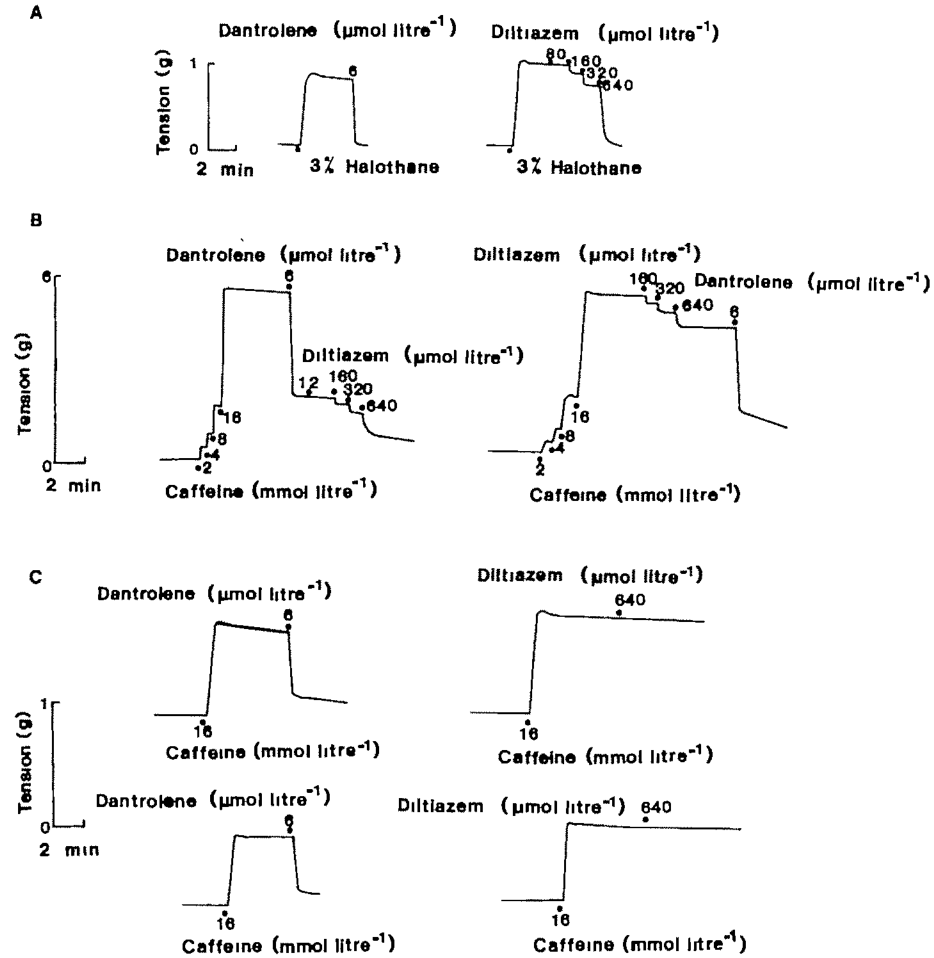

FIG. 3. The antagonistic effects of diltiazem and dantrolene on contractures from MHS and control muscle. A: Effect of diltiazem and dantrolene on 3% halothane-induced contractures. B Effect of diltiazem and dantrolene on caffeine-induced contractures in MHS preparations. Similar responses were obtained in control preparations. C: Effect of dantrolene and diltiazem on caffeine contractures in detubulated MHS preparations (top) and detubulated control preparations (bottom)

($n = 5$) preparations by 86 (12)% and 86 (11)%, respectively, in less than 2 h. Increasing the concentration of dantrolene to 12 μmol litre^{-1} did not have any further effect on twitch height (fig. 1). Similar responses were obtained in control tissue.

Effect of diltiazem and dantrolene on contractures induced by halothane, caffeine and potassium chloride

Pretreatment of MHS preparations with diltiazem 80 μmol litre^{-1} or dantrolene 6 μmol litre^{-1} significantly inhibited contractures induced by 3% halothane ($n = 10$ and 11, respectively) and potassium chloride 80 mmol litre^{-1} ($n = 20$ and 8, respectively) (table I). Caffeine 1–16 mmol litre^{-1} caused concentration-dependent contractures of MHS fibres that were significantly greater than those in control preparations (fig. 2A). At higher concentrations (24–32 mmol litre^{-1}), contractures were not significantly different.

Contractures induced by caffeine 4–64 mmol litre^{-1} in control preparations in the presence of diltiazem or dantrolene are shown in figure 2B. All were reduced significantly in preparations pretreated with dantrolene 6 μmol litre^{-1}. Diltiazem 80 μmol litre^{-1} also reduced significantly the contractures produced by caffeine 4–24 mmol

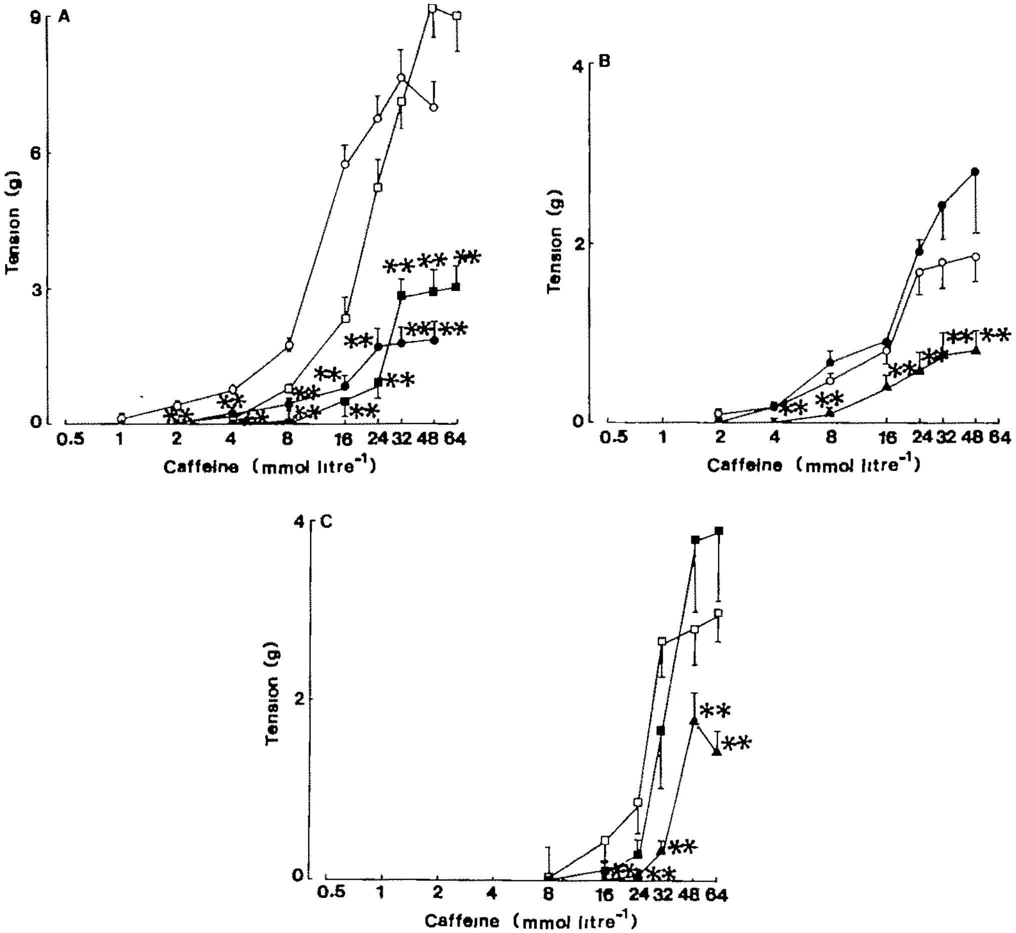

FIG 4. Cumulative concentration–effect curves (mean (SEM)) to caffeine in isolated MHS (○) and control (□) porcine skeletal muscle preparations. A: MHS and control before (○, □) and after (●, ■) glycerol-induced detubulation. B: Effect of diltiazem 80 µmol litre^{-1} (●) and dantrolene 6 µmol litre^{-1} (▲) on caffeine-induced contractures in detubulated MHS preparations. C Effect of diltiazem 80 µmol litre^{-1} (■) and dantrolene 6 µmol litre^{-1} (▲) on caffeine-induced contractures in detubulated control preparations Number of observations for both MHS and control preparations: 14–18 (separate fibre preparations for untreated strips); 8–10 (dantrolene or diltiazem pretreated strips) Significant differences: $^{**}P < 0.01$

litre^{-1}, but failed to alter significantly the tension generated by greater concentrations (32 and 48 mmol litre^{-1}). The effect of diltiazem 80 µmol litre^{-1} or dantrolene 6 µmol litre^{-1} on caffeine contractures in MHS preparations was similar to that observed in control preparations (fig. 2C). Diltiazem decreased significantly contractures to caffeine 1.0–24 mmol litre^{-1}, but failed to alter contractures at higher concentrations (32 and 48 mmol litre^{-1}). A significant decrease in contractures produced by caffeine 1–32 mmol litre^{-1} was observed in preparations pretreated with dantrolene.

Antagonistic effects of diltiazem and dantrolene on contractures induced by halothane and caffeine in MHS and control muscle

Dantrolene 6 µmol litre^{-1} antagonized contractures in MHS muscle induced by 3 % halothane (fig. 3A), but greater concentrations of diltiazem (640 µmol litre^{-1}) were required to antagonize contractures to halothane (fig. 3A). In MHS and control preparations diltiazem 640 µmol litre^{-1} and dantrolene 6 µmol litre^{-1} completely antagonized contractures produced by caffeine 4 mmol litre^{-1} (results not shown). At higher concentrations of caffeine (16 mmol litre^{-1}), dantrolene 6 µmol litre^{-1} and diltiazem 640 µmol litre^{-1} partially antagonized induced tension in MHS muscle (fig. 3B). However, dantrolene 6 µmol litre^{-1} still antagonized contractures induced by caffeine 16 mmol litre^{-1} ($n = 8$) after diltiazem 640 µmol litre^{-1}-induced antagonism and *vice versa* (fig. 3B). Increasing the concentration of diltiazem (> 640 µmol litre^{-1}) or dantrolene (> 6 µmol litre^{-1}) failed to induce further antagonism. This was also observed in control preparations.

Effect of glycerol-induced detubulation on caffeine contractures in the absence and presence of diltiazem and dantrolene

Twitch response was abolished in all detubulated fibres before contractures were superimposed. All caffeine contractures were reduced significantly in MHS and control detubulated muscle fibres (fig. 4A). The hypercontractility of MHS preparations to caffeine was abolished. Dantrolene 6 µmol litre^{-1} significantly reduced, while diltiazem 80 µmol litre^{-1} had no effect on, contractures induced by caffeine in detubulated MHS (fig. 4B) and control preparations (fig. 4C).

Diltiazem 640 µmol litre^{-1} also failed to antagonize contractures to caffeine 16 mmol litre^{-1} in MHS ($n = 6$) (fig. 3C) and control ($n = 6$) (fig. 3C) detubulated fibres, while dantrolene 6 µmol litre^{-1} induced antagonism in both preparations.

DISCUSSION

Diltiazem inhibited twitch response and the characteristic hypercontractility of MHS muscle to halothane, caffeine and potassium chloride. Contracture responses to caffeine and electrical stimulation also were depressed by diltiazem, in control preparations. Calcium channel antagonists bind preferentially to voltage operated calcium channels located in the T-tubular membranes of skeletal muscle [5] and inhibit Ca^{2+} influx [4, 7, 14]. Although the role of extracellular Ca^{2+} in the activation of contractile activity in skeletal muscle remains unknown, Ca^{2+} entering from the external solution has been shown to contribute significantly to the development of contracture [7, 15] and may be required during contractile activity when Ca^{2+} release from the SR becomes inadequate [16]. Diltiazem may inhibit contractile responses by suppressing Ca^{2+} influx at the level of the T-tubular membrane. Such Ca^{2+} currents may be activated during the sustained contractile activity which is observed throughout an MH episode. Ca^{2+} entering the muscle cell through Ca^{2+} channels in the T-tubule membrane may, therefore, play an important role in the aetiology of the MH syndrome.

High concentrations of diltiazem (80 µmol litre^{-1}) were required to inhibit contracture responses, which may not be entirely consistent with diltiazem acting solely on Ca^{2+} channels. However, high concentrations (> 20 µmol litre^{-1}) of calcium channel antagonists are often required to induce an effect on skeletal muscle contractility [17]. For example, Almers and McCleskey [14] reported an IC_{50} of 80 µmol litre^{-1} for diltiazem in voltage clamp experiments using frog skeletal muscle, and in mammalian skeletal muscle preparations diltiazem 63 µmol litre^{-1} was required to produce a 50% decrease in Ca^{2+} currents [18]. A poor correlation between studies of binding to isolated Ca^{2+} channels (K_d in the nmol litre^{-1} range) [19, 20] and *in vitro* functional studies is often observed in skeletal muscle, and may indicate not only non-specific effects, but also poor diffusion into muscle preparations along T-tubular membranes.

Caffeine may induce contractures in skeletal muscle by acting at the level of the T-tubular membrane [21] in addition to inducing Ca^{2+} release directly from the SR [22]. Suppression of responses to caffeine in detubulated fibres support these views [23]. Modification of caffeine-induced contractures by diltiazem is consistent, therefore, with the calcium channel antagonists acting at the level of the T-tubular membrane to inhibit Ca^{2+} influx. Furthermore, diltiazem failed to inhibit or antagonize caffeine contractures in detubulated muscle preparations.

Dantrolene also effectively inhibited and antagonized the abnormal contractures produced by a variety of chemical stimuli in MHS fibres, consistent with previous reports [2]. The skeletal neuromuscular blocking drug acts primarily to decrease myoplasmic Ca^{2+} concentration by suppressing excitation–contraction coupling at some element of the triadic junction. Dantrolene may act at the level of the T-tubular membrane or bind to Ca^{2+} channels at the junctional region of the SR [9]. Antagonism of caffeine-induced contractures by diltiazem in the presence of maximal effective concentrations of dantrolene, and *vice versa*, suggests that diltiazem and dantrolene modify contracture at different sites. Diltiazem may inhibit Ca^{2+} influx associated with the voltage operated calcium channels of the T-tubular membrane, while dantrolene may inhibit Ca^{2+} release directly from the SR.

Much greater concentrations of diltiazem (80–640 μmol litre^{-1}) than of dantrolene (6 μmol litre^{-1}) were needed to inhibit and antagonize pharmacologically induced contractures. This suggests that dantrolene is a more potent treatment for MH than is diltiazem.

An abnormality in the mechanism of excitation–contraction coupling has been proposed to result in an increased myoplasmic concentration of Ca^{2+} in MHS muscle [2,3]. Inhibition of contractile responses by diltiazem and dantrolene support this view and incriminate events of coupling which involve the T-tubular membrane, such as signal transmission at the triadic junction and Ca^{2+} release from the SR.

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Br. J. Anaesth. (1989), **62**, 573–575

PLASMA CONCENTRATIONS OF CATECHOLAMINES FOLLOWING INTRAOCULAR IRRIGATION WITH ADRENALINE

D. FELL, A. P. WATSON AND N. HINDOCHA

SUMMARY

Plasma concentrations of adrenaline and noradrenaline were measured in 13 patients undergoing cataract surgery after intraocular irrigation with an adrenaline-containing solution. Venous blood samples were withdrawn before, during and after intraocular irrigation with a solution of adrenaline 1:500000. Plasma concentrations of both adrenaline and noradrenaline did not differ significantly from those noted before induction of anaesthesia.

During extracapsular or intracapsular cataract extraction in ophthalmic surgery, the remnants of the opacified lens are removed from within the capsular area by aspiration. The volume of the anterior chamber is maintained by simultaneous irrigation with a solution of Ringer's lactate. This procedure demands a widely dilated pupil and, whilst dilatation is easily obtained before operation, the pupil may begin to constrict during the procedure. To counteract this tendency, adrenaline 1 mg is added to 500 ml of the irrigating solution. Although most of the solution is flushed out of the eye and the amount of drug available is likely to be small, some absorption may occur. Indeed, caution has been recommended when adrenaline is used in the conjunctiva, following a report of rapid absorption in a child [1].

The majority of patients undergoing cataract surgery are elderly, and absorption of exogenous adrenaline may be harmful. This study has investigated the extent of absorption of adrenaline during cataract surgery.

METHODS AND RESULTS

Following informed consent, and the approval of the District Ethics Committee, we studied 13 patients (M:F 3:10) undergoing cataract surgery. Patients receiving tricyclic or monoamine oxidase inhibitor antidepressants were excluded from the study. Premedication comprised diazepam 5–10 mg and droperidol 5 mg by mouth. In the anaesthetic room, after local anaesthesia, an 18-gauge cannula was inserted in the antecubital fossa to permit blood sampling. General anaesthesia comprised fentanyl 1 μg kg^{-1}, thiopentone 3–5 mg kg^{-1}, and 67% nitrous oxide in oxygen. Neuromuscular block was accomplished with vecuronium 0.1 mg kg^{-1} and, after tracheal intubation, the patient's lungs were ventilated with an appropriate fresh gas flow to maintain normocapnia. No volatile agent was used. The ECG was monitored continuously and arterial pressure was measured non-invasively using a "Copal" semi-automatic sphygmomanometer.

Venous blood samples (10 ml) were obtained: before induction of anaesthesia, 10 min after tracheal intubation before the start of irrigation, 2 min after the start of irrigation, at 5-min intervals during irrigation, and 5 min after cessation of irrigation. Arterial pressure and heart rate were recorded at corresponding times and any arrhythmias were noted. Blood samples were centrifuged and the plasma separated and stored at −70 °C before assay of catecholamines by high pressure liquid chromatography [2]. Irrigation during surgery was accomplished using a solution

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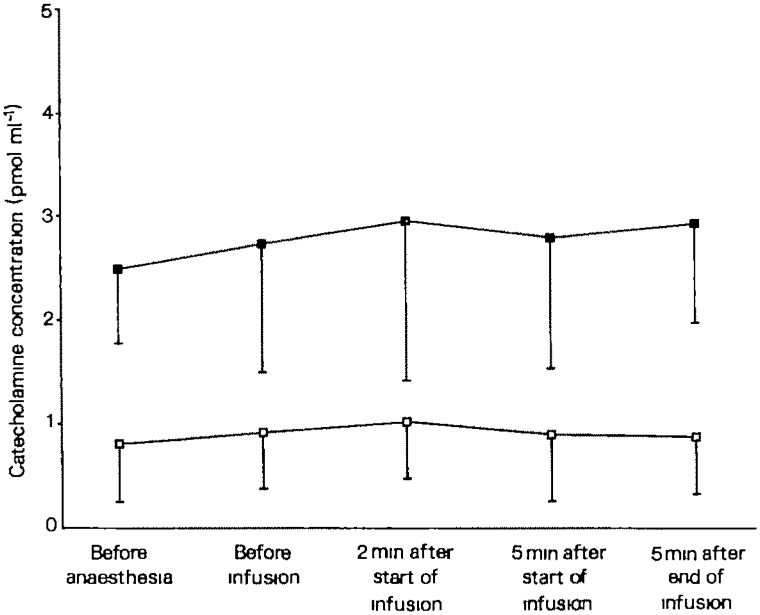

FIG. 1. Mean (SD) catecholamine concentrations (pmol ml^{-1}). ☐ = Adrenaline, ■ = noradrenaline.

of Ringer's lactate 500 ml containing adrenaline 1:500000, 1 mg.

The mean (SD) age of the patients was 68.2 (7.9) yr (range 49–80 yr), weight was 59 (13.5) kg (range 50–90 kg), and the quantity of adrenaline used (calculated from the amount of unused infusion) was 81.5 (27.33) μg.

The plasma concentration of adrenaline did not differ significantly, during or after the infusion, from the baseline value of 0.81 pmol ml^{-1} (analysis of variance). A similar pattern was observed in respect of noradrenaline concentration, for which the mean (SD) baseline concentration was 2.49 pmol ml^{-1} (fig. 1).

In comparison with the mean (SD) baseline measurement of 69.3 (14.0) beat min^{-1}, heart rate increased after induction to 74.8 (15.8) beat min^{-1}, but remained unchanged thereafter. Mean (SD) systolic arterial pressure at baseline was 156.3 (30.8) mm Hg and this decreased to a minimum of 139.5 (40.5) mm Hg 5 min after irrigation. No arrhythmias were noted during the operative period in any patient.

COMMENT

Our data suggest that significant absorption of adrenaline does not occur after intraocular irrigation of adrenaline-containing solutions during cataract surgery.

In our study the maximum dose of adrenaline administered was approximately 1.3 μg kg^{-1} (this is subject to a small error because of spillage). In contrast, Taylor, Achola and Smith [3] found that plasma concentration of adrenaline increased by 300% after submucous injection of a dose of 0.4 μg kg^{-1}, whilst Donlon and Moss [4] observed an increase in adrenaline concentration of 190% after a dose of adrenaline 0.8 μg kg^{-1} was administered by the retrobulbar route.

Absorption of adrenaline from an intraocular irrigating solution may occur by four routes: the trabecular meshwork leading to the canal of Schlemm and episcleral veins, the anterior face of the ciliary body and suprachoroidal route, the vasculature of the iris, and by transconjunctival absorption of overflow from the corneal incision. Absorption is affected by the extent of vascular perfusion of the eye and conjunctiva and this is influenced by the anaesthetic technique. For example, hypocapnia reduces blood flow in this area.

A previous study has shown that a single intraocular injection of adrenaline 40–700 μg did not produce cardiac arrhythmias in adults during halothane anaesthesia [5]. The present study has shown that significant absorption of adrenaline did not occur during intraocular irrigation of adrenaline 1.3 µg kg^{-1}.

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Br. J. Anaesth. (1989), **62**, 576–577

PERIOPERATIVE COMPLICATIONS FOLLOWING THE USE OF VANCOMYCIN IN CHILDREN: A REPORT OF TWO CASES

C. J. BEST, M. EWART AND E. SUMNER

SUMMARY

We describe two patients in whom rapid administration of vancomycin caused severe hypotension. Possible mechanisms for this effect are discussed, with reference to the role of the anaesthetist as administrator of drugs prescribed by others. Recommendations are made on safe administration of vancomycin with respect to rate of infusion and possible interactions.

Vancomycin is an aminoglycoside antibiotic with activity against gram-positive organisms, in particular *Staphylococcus pyogenes* (including strains resistant to benzylpenicillin and methicillin) and Streptococci. It has been recommended for use in the prophylaxis of endocarditis in patients who are allergic to penicillin [1], with the dose being administered by slow i.v. infusion over a minimum time of 60 min. However, if given inadvertently at a faster rate, it may cause potentially fatal consequences. We describe two patients in whom bolus injection of vancomycin caused severe systemic reactions.

CASE REPORTS

Patient No. 1

An 11-yr-old boy presented for inguinal hernia repair and orchidopexy; he had undergone previous surgery to his pulmonary valve. He was allergic to penicillin. Because of an oversight, he arrived in the anaesthetic room without any antibiotic prophylaxis against endocarditis. Anaesthesia was induced with thiopentone and suxamethonium, the trachea intubated and the patient allowed to breathe a nitrous oxide–oxygen–halothane mixture. On the advice of the Microbiology Department, the following antibiotics were administered: metronidazole 7.5 mg kg^{-1}, gentamicin 2 mg kg^{-1} and vancomycin 20 mg kg^{-1}. The first two were given uneventfully. However, the vancomycin was given over a period of only 2 min. During the course of the next 1 min the systolic arterial pressure decreased to 50 mm Hg and oxygen saturation to 80%. A rash was noticed, extending over the head and neck, and there was a degree of bronchospasm. The patient's lungs were ventilated with 100% oxygen and he was given aminophylline with hydrocortisone i.v. He made a quick recovery, and awoke rapidly at the end of anaesthesia with no ill effects. He was discharged home the next day.

Patient No. 2

A 2-month old child presented for repair of coarctation of the aorta. He had been admitted 4 days before the day of operation with pulmonary infection, and was undergoing artificial ventilation. Because of severe hypertension as measured by cuff on the right arm (pre-coarctation) he was receiving propranolol 1 mg kg^{-1} by mouth three times a day. Approximately 20 min before he was brought to theatre, a vancomycin infusion, intended to be given over the 60 min preceding anaesthesia, was started. On arrival in the anaesthetic room he was noted to be cyanosed, with absent pulses and heart sounds. His colour quickly returned with cardiac massage

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and the administration of bicarbonate; arterial blood-gas analysis at this point was essentially normal. It was discovered subsequently that the whole dose of vancomycin had been given over only 20 min.

DISCUSSION

These two case reports illustrate the dangers of rapid administration of vancomycin. In the first patient, the mechanism of the circulatory and ventilatory collapse was probably an anaphylactoid type reaction, with the clinical features of histamine release being manifest. In the second patient, a milder reaction took place as no maculopapular rash was seen and there was no bronchospasm. Nonetheless, because of beta-blockade, the hypotensive effect of the vancomycin infusion may have been more pronounced than otherwise.

A recent review [2], together with case reports have highlighted the dangers of vancomycin when given rapidly. In addition, a particular presentation has been described, the "Red Man's Syndrome" [3], characterized by profound hypotension, often with a maculopapular rash over the face, neck, upper chest and extremities. Cardiac arrest also has been attributed to rapid infusion of vancomycin 1 g over 2 min [4]. The first patient serves to illustrate this well known presentation of vancomycin toxicity. The second patient highlights the dangers of interactions with other drugs, in this case a beta blocking agent.

There has also been a report of hypotension and rash in a 10-yr-old child with Down's syndrome and congenital heart disease after vancomycin had been infused over a period of 10 min [5]. Although the systolic arterial pressure in this instance decreased from 90 to 40 mm Hg, there was a compensatory increase in heart rate from 120 to 150 beat min^{-1}, which would have been prevented by beta-blockade.

Vancomycin is often used in the treatment or prophylaxis of infection in patients with cardiac disease, and so the scope for drug interactions is large. On informal questioning, approximately 50 % of those members of staff who prescribed or administered the drug, whilst aware of the recommendations on speed of administration, were not aware why these were in force and did not know of the dangers described above.

This raises the question of the anaesthetist's responsibility when giving drugs prescribed by other medical staff. This situation arises when antibiotics are given at induction or during operation. Although the drugs are not directly relevant to the anaesthetic, the principle that the administrator of a drug is responsible for its actions and side effects still holds. This may be a critical time as far as interactions are concerned, with the anaesthetist's attention being potentially drawn to other more pressing matters. As a result, interactions such as those described in the first patient may occur. The anaesthetist must be fully conversant with the actions of any drug he administers, even if it has been prescribed by other medical staff.

We recommend that infusions of vancomycin should be monitored carefully by trained personnel, and that a volumetric pump be used in order to ensure that the drug is given at the correct rate, especially in view of the small volumes that are used in paediatric practice. Furthermore, in the case of preoperative prophylaxis, if the infusion has not been completed by the start of anaesthesia, induction should be delayed, as it has been suggested that vancomycin may interact directly with anaesthetic agents [6]. Special care should be taken when patients are receiving other drugs which depress cardiovascular function.

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Br. J. Anaesth. (1989), **62**, 578–581

CORRESPONDENCE

LIMITATIONS OF ADRENALINE TEST DOSES IN OBSTETRIC PATIENTS UNDERGOING EXTRADURAL ANAESTHESIA

Sir,—In a recent editorial on extradural test doses for use in the detection of inadvertent intravascular injection, Scott [1] suggested the use of adrenaline in obstetric patients However, the value of this technique has not been confirmed experimentally.

In a study including patients in labour, Leighton and others [2] administered either physiological saline or adrenaline i.v. in order to assess the effects of intravascular injection of adrenaline. For a positive response, they used the criteria of an increase in maternal heart rate of greater than 25 beat min^{-1} compared with that at the time of injection, occuring within 2 min of injection and lasting for more than 15 s, as determined by continuous electrocardiographic monitoring. Two of 10 patients receiving saline were found to fulfil these criteria compared with five of 10 in the adrenaline group; this difference was not statistically significant Furthermore, two of the 10 patients receiving adrenaline developed signs of fetal distress.

I.v. adrenaline has been shown to cause decreased uterine blood flow in pregnant guineapigs [3] and sheep [4]. Thus the use of an adrenaline test dose in obstetric patients is not to be recommended.

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Sir,—I am obliged for the opportunity to comment upon the letter of Dr Sosis. He is quite correct to draw attention to the difficulty of using a fixed criterion after an extradural test dose, and expecting the results to be unequivocal.

Variations in heart rate of this order occur without any injection of drug, particularly in nervous subjects. In the study of Leighton and colleagues [1], mothers in labour were fully informed of the study; therefore, it is not difficult to understand that large variations in heart rate occurred before any of the injections in some mothers. However, the authors stated that their "blinded" observer, who was watching both the mothers and their monitors, was able to distinguish quite accurately all the i.v. adrenaline injections; I suppose that this was because he was enquiring also of *subjective* effects.

Perhaps more serious is the suggestion that adrenaline 15 µg i v., given as a test dose, is potentially dangerous for the fetus. Two fetuses showed heart rate abnormalities for 10–15 min after injection of adrenaline, one with deceleration during uterine contractions and one with a minor bradycardia and loss of beat-to-beat variability. Both babies were normal at birth. The conclusion that these changes resulted from reduced uterine blood flow (and they may well have been) is supported by two studies, both of which showed reductions of 20–40 % after i.v. boluses of adrenaline [2,3] Hood and colleagues [3] commented that the measured reduction in uterine blood flow was similar to that which occurs with a uterine contraction. This puts the problem into better perspective. One would like to know how a dose of adrenaline 15 µg compares with the output of endogenous adrenaline from the nervous mother during an unpleasant labour.

Adrenaline i.v. will be given only to those mothers in whom the extradural catheter has been misplaced in a vein. If *no* test dose is given because of concern for the neonate, three to seven times that dose will be given as the therapeutic dose if adrenaline is added to the local anaesthetic (the common practice in the United States).

One of my main points was to impress upon anaesthetists that test doses were not unequivocally diagnostic of correct or incorrect placement. Moreover, a negative test should be treated with caution, and is certainly not a licence to inject a large dose of drug rapidly.

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Sir,—Dr Scott is correct to highlight the uncertainty surrounding the use of extradural test doses [1], but he offered no evidence either to support or to reject the value of added adrenaline in labouring patients. As a supporter of the value of extradural "test" doses or a small-volume preliminary injection before each top up, I would argue that subarachnoid injection may be detected with confidence, but intravascular injection cannot. The former does occur, although very rarely. The latter has not occurred in the Queen Mother's Hospital in 24 years of extradural practice and would appear equally rare in other institutions. Nevertheless, intravascular injection has been reported in the U.S.A. Therefore, any test designed to detect intravascular placement of an extradural catheter must be both extremely sensitive and very specific; the available evidence suggests that the addition of adrenaline to the test dose is not.

Moore and Batra [2] studied the effect of adrenaline 15 μg i.v., added to local anaesthetic solution in sedated, non-pregnant patients and noted a heart rate (HR) increase of 30 beat min^{-1} with an onset time of 23 s and lasting 10 s. In labouring patients, following the injection of a test dose of extradural bupivacaine *without* added adrenaline, a false positive test was noted in 12 % [3]. Using an i.v injection of saline both with and without the addition of adrenaline 15 μg in labouring patients Leighton [4] observed that only 50 % of patients given adrenaline had an increase in HR of more than 25 beat min^{-1} lasting more than 15 s Our own observations in patients whose ECG was monitored continuously following insertion of an extradural catheter, but before injection of local anaesthetic solution, confirmed a coefficient of variation in HR of 76 %.

This evidence suggests that the addition of adrenaline to the test dose is of little value and cannot be recommended as it is insensitive and non-specific. Indeed, in a review article on the same subject, Dain, Rolbin and Hew [5] concluded that the addition of adrenaline appeared to create more problems than its solves.

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Sir,—Dr Thorburn takes me to task for many of the same reasons as Dr Sosis, although I was at pains to describe in the editorial all the problems of interpreting adrenaline-containing test doses. I would dispute, however, the frequency of accidental i.v. injection. In a recent survey of complications associated with extradural block in obstetrics carried out by the College of Obstetricians and Gynaecologists and the College of Anaesthetists (to be published), 20 cases of acute toxic reactions were reported, compared with eight with an unexpected high or total spinal block; so it is not a complication peculiar to the United States.

Accidental i.v. placement of the needle/catheter is notoriously more difficult to diagnose than accidental subarachnoid placement, when CSF usually gushes from the needle. The Queen Mother's Hospital is to be congratulated on its 24-years experience, but should not extrapolate too widely. It is as well to remember that serious harm from i.v. misplacement is likely to occur only with the doses used for Caesarean section, not with those used for pain relief

D B. SCOTT
Edinburgh

EXTRADURAL BUPIVACAINE AND METHADONE FOR EXTRACORPOREAL SHOCK-WAVE LITHOTRIPSY

Sir,—Drenger and colleagues [1] claim that their proposed regimens for extracorporeal shock wave lithotripsy (ESWL) provided haemodynamic stability, but it is unfortunate that the cardiovascular data presented appear to be confined to the periods following establishment of extradural blockade and immersion in the water bath. This point is crucial because ESWL (as practised on the Dornier HM3 Lithotripter) requires the patient to be strapped to a hoist in the semi-recumbent position with the legs partially jack-knifed, before immersion in the water bath. Significant postural hypotension may be induced; in our experience [2,3] the most dramatic changes in arterial pressure are observed invariably during the period before immersion, as the hydrostatic pressure which is exerted subsequently on the lower half of the body tends to cause partial reversal of the hypotension

Thus while decreases in systolic arterial pressure from baseline values of 8.9 % and 12.6 % were observed following establishment of sensory blockade to T3–T6 in two groups of patients undergoing spinal and extradural analgesia respectively [2], further decreases of 23.0 % and 21.2 % were observed immediately after placement in the hoist. The observed decreases from baseline following subsequent bath immersion were 12.3 % and 11.6 %, respectively, indicating that the systolic arterial pressures had increased relative to the values recorded after hoist placement and before bath immersion.

These figures indicate clearly that haemodynamic observations during ESWL which do not specifically focus on the period immediately after hoist placement may produce misleading conclusions.

M LIM
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Sir,—Thank you for the opportunity to reply to Dr Lim's letter. We agree that the paragraph which describes the haemodynamic changes can be misinterpreted [1] The data on arterial pressure changes are presented in the article. We showed that the use of a low dose of 0.5 % bupivacaine 8–14 ml, resulted in minimal (4.7%) reduction in systolic arterial pressure. Similar results (5.5% reduction) were shown when methadone was added to the local anaesthetic drug.

These changes in arterial pressure were observed before immersion in the water bath, including the period of placing the patient in the hydraulic cradle. The patients could move themselves to the cradle almost unassisted, as motor function was only slightly affected. Ephedrine 5–10 mg i.v was required in 7 of 144 (4.8%) patients to correct hypotensive episodes. The article cited by Dr Lim [2] showed that, using 0.5% bupivacaine 15–25 ml, a much higher rate of hypotensive episodes occurred and i.v. ephedrine had to be used in 23% of the patients. The stage of body immersion in warm water was accompanied by a small and statistically insignificant increase in systolic arterial pressure in most of the patients in our study.

B DRENGER
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PARKINSONISM AND THE ANAESTHETIST

SIR,—The effects of neuromuscular blocking drugs on patients with neuromuscular disorders have always been interesting to anaesthetists. In an excellent review on Parkinsonism and the anaesthetist [1], Severn cited the only reported case of hyperkalaemia after suxamethonium in a patient with Parkinson's disease [2], presumably of the idiopathic type. However, because of the absence of other similar reports, doubts have been expressed on whether or not the patient had hyperkalaemia for other reasons. Azar [3] suggested that, as the patient had undergone two lumbar laminectomies for low back pain with the possibility of muscular denervation, the hyperkalaemia could have resulted from potassium release from denervated muscles rather than Parkinsonian muscles.

I measured serum potassium and arterial blood-gases before and after administration of suxamethonium in a 54-yr-old, 58-kg female with long-standing Parkinsonism secondary to use of neuroleptic drugs (table I). She was otherwise healthy and required a mandibular alveoplasty. In the previous 4 months she had twice undergone general anaesthesia; the usual clinical doses of suxamethonium and pancuronium had been given, with no unusual effect detected. Anaesthesia was induced with fentanyl 0.15 mg, thiopentone 250 mg and suxamethonium 80 mg. Nasotracheal intubation and recovery from muscle paralysis were totally uneventful.

The blood-gas and serum potassium data were compatible with previously published data. Cooperman [4], in an unspecified number of Parkinsonian patients, observed insignificant changes in serum potassium concentrations after suxamethonium and the results of the regional curare test on eight Parkinsonian patients (aetiology not specified) were found to be within normal limits [5]. Nevertheless, until more conclusive evidence attesting to its safety is available, I am in agreement with Dr Severn in urging caution in the use of suxamethonium in patients with Parkinson's disease. Moreover, as with any neuromuscular disorder, neuromuscular function should be monitored when neuromuscular blocking drugs are administered to patients with Parkinsonism

A M-H. HO
St Catharines, Ontario

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SIR,—Two questions should be asked of this report by Dr Ho of suxamethonium-induced hyperkalaemia in a patient with Parkinsonism. First, could the hyperkalaemia have resulted from any other cause? Second, is there any independent evidence of a functional change in the neuromuscular junction that might lead one to expect an abnormal response to suxamethonium?

In his case report, Gravlee [1] discussed the possible reasons for an increase in serum potassium from 4.2 to 7.6 mmol litre^{-1} following the infusion of suxamethonium 800 mg. He concluded that the most likely explanation lay in the effect of Parkinsonism on the modulation of lower motor neurone activity.

Sica and colleagues [2] provided evidence of changes in the neuromuscular junction in Parkinsonism. They demonstrated abnormally large muscle action potentials in the extensor

TABLE I. *Serum potassium concentrations and arterial blood pH before and after suxamethonium*

	Before induction of anaesthesia	After intubation		
		2 min	8 min	25 min
Serum potassium (mmol litre^{-1})	4.0	4.1	4.0	3.8
Arterial blood pH	7.37	7.40	7.44	7.43

digitorum brevis and calculated that there is a reduction in the number of functioning motor units of the deep peroneal nerve. They suggested that undamaged motor neurones take over the function of adjacent damaged nerves, and that this damage occurs because of the loss of some trophic influence from higher centres.

There would seem, therefore, to be adequate cause to justify Gravlee's concern. The question of reproducibility of results is a different matter. Sica and colleagues claimed that the reduction of functioning motor units occurs most rapidly in the first 9 months of the disease (although they acknowledged the difficulty of defining the onset of Parkinsonism). Gravlee's patient had long standing and well controlled Parkinsonism, the symptoms of which worsened rapidly on withdrawal of L-Dopa 5 days before surgery. Is it possible that clinical deterioration was associated with an acute loss of functioning lower motor neurones, with a predictable response to suxamethonium? It would be worth adding this complication to the list of dangers of abrupt preoperative withdrawal of L-Dopa.

A. M. SEVERN
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PROSTAGLANDINS AND THE LOWER OESOPHAGEAL SPHINCTER

Sir,—The paper by Jones and colleagues [1] considered lower oesophageal sphincter (LOS) tone in a group of patients undergoing suction termination of pregnancy. All those studied had been given gemeprost, and although the possible effect of prostaglandins on the LOS was mentioned, it was not explored fully in the paper.

Prostaglandins of the E group are known to relax circular smooth muscle in the gastrointestinal tract of humans and some animals, with the consequent effect of lowering the LOS tone [2]. Prostaglandins of the F group, however, are excitatory to this group of muscles, and therefore cause LOS pressure to increase [3].

Furthermore, indomethacin has been shown to increase the tone of the LOS in human subjects [3], possibly because of its inhibitory effect on prostaglandin synthetase, leading to a reduction in endogenous prostaglandin E within the LOS muscle.

Gemeprost is a prostaglandin E_1 analogue, and although its effect on the cervix is mainly by a local action, some systemic absorption must occur also To rule out any effect this may have on the LOS tone, it would be interesting to know the results of a similar study in a comparable group of patients not given gemeprost.

A. MAHONEY
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Sir,—Thank you for giving us the opportunity to reply to Dr Mahoney's letter. We welcome his comments regarding the effects of prostaglandins on the LOS. Gemeprost, a prostaglandin E_1 analogue is now used almost universally in the first trimester before termination of pregnancy because of its beneficial local action on the cervix. The effects of this agent on the LOS are unknown and we would agree that a study comparing barrier pressures in a group of patients not given gemeprost would be of interest.

M. J. JONES
R. W. D. MITCHELL
Leicester

Br. J. Anaesth. (1989), **62**, 582–584

BOOK REVIEWS

Obstetric Anesthesia: The Complicated Patient, 2nd Edn. Edited by F. M. James III, A. S. Wheeler and D. M. Dewan. Published by F. A. Davies Co. Pp. 577; indexed; illustrated. Price $98.75.

Continuing advances in obstetric care, medicine and surgery, coupled with the high expectation of women of child bearing age means that the obstetric anaesthetist is presented with even greater challenges in the maternity unit. There is also a general acceptance by the medical profession that the anaesthetist is an integral part of the obstetric team caring for the complicated patient. Consequently the haematologist, cardiologist, diabetologist and a multitude of other specialists will expect the anaesthetist to be well informed.

The success of the first edition of this book and the advances, both technical and theoretical, in the care of the complicated obstetric patient have stimulated a new edition. The editors have responded to clinical and social changes in our obstetric population by introducing new chapters, for example "*in vitro* fertilization", "obesity", "extremes of age: the teenager and the elderly parturient".

The editors have enlisted experts in various aspects of obstetric anaesthesia to contribute chapters, which accounts for the excellence of the book. Each chapter commences with a short introduction and ends with the author's own summary of salient points, which is most helpful. The reference section at the end of each chapter is exhaustive. The book contains 27 chapters and is divided into five parts. Parts 1 and 2 are the weakest and possibly will not be referred to as frequently as subsequent sections, since they describe what could be regarded as "normal" obstetric anaesthesia. Nevertheless, many general anaesthetists would benefit by reading the section on the anaesthetic management of the incompetent cervix.

Part 3 is Maternal Problems by system. This section is excellent and merits thorough perusal by all obstetric anaesthetists. Each chapter is a mine of information on rare and not so rare problems, for example epilepsy, congenital heart disease, asthma, cystic fibrosis, renal disease, herniated lumbar disc, anaemias, leukaemias, coagulation disorders and a host of other fascinating problems. This whole section could profitably be studied by our obstetric colleagues too!

The general acceptance of extradural analgesia and confidence with which it is managed is reflected by the widespread indications. The use of continuous extradural infusions of 0.12% bupivacaine with or without additional opioid is frequently recommended. The importance of adequate monitoring and prompt resuscitation of the patient with an obstetric emergency is continually emphasized. Advances in intensive care profit the obstetric patient, but I doubt that many U.K. obstetric anaesthetists would reach for the Swan–Ganz so readily as their North American counterparts.

The section on fetal problems reflects changing attitudes to the management of the premature infant and fetal distress. Perusal of these chapters will enable the practising obstetric anaesthetist simultaneously to be "guardian of the mother's welfare" and to aid delivery of an infant in optimum condition.

Part 5 is a miscellany of problems—diabetes, hypertension, obesity, *in vitro* fertilization, etc. Few anaesthetists in the U.K. will acquire much experience of trauma, non-obstetric surgery, and substance abuse in the pregnant patient. These chapters are excellent for reference.

This book is a mandatory purchase for all obstetric anaesthetic departments. Many anaesthetists, especially those working in regional and supra-regional referral centres may wish to have their own personal copy, to which they will frequently refer as the complicated patient presents for obstetric anaesthetic care.

R. MacDonald

Yearbook of Critical Care Medicine, 1988, 6th Edn. Edited by M. C. Rogers. Published by Year Book Medical Publishers Inc., Chicago, London. Pp. 466; indexed, illustrated. Price £34.

This sixth edition of the *Yearbook* has reviewed articles published between August 1986 and July 1987; each article is represented by an abstract with tables or graphs, and there then follows a critical review. Ninety-four journals have been reviewed during this period. Omitted from the journal list are *Anaesthesia* and *Transplantation Proceedings*, both of which could usefully have been included.

The reviewers comprise eight American intensive care specialists, six of whom are also anaesthetists. Although the choice of articles depends on the material available to them, it is also affected by a transatlantic perspective of what is important. This latter factor may account for the absence of any articles on selective decontamination, pulmonary colonization, gastric pH and bacterial overgrowth, or techniques of sedation for ventilation, there are only two articles on analgesia in the critically ill, and these examine extradural analgesia in relation to surgery. There is only one article referring to haemodialysis and one to haemofiltration, and CAVHD does not yet make an appearance. There are numerous articles referring to calcium channel blockers and their effects on cerebral and myocardial ischaemia, but there is no discussion on gut blood flow and the role of the gut in the release of endotoxin.

With these caveats, the majority of articles chosen are interesting and relevant, and the reviewers' comments are pertinent and enjoyable to read. Occasional articles are selected for their faults, and this is important also as an education in critical analysis. Socio-economic issues are addressed well. Trauma, pulmonary pathophysiology, ventilation and cerebral haemodynamics are all presented adequately and analysed.

This *Yearbook*, in common with its predecessors, will appeal to the specialist in critical care, particularly to those with research interests. Even those with catholic reading habits will find new material. The format makes it easily digestible, and it is a reasonable choice for bedside reading. It is not likely to be a useful reference for large libraries, but smaller libraries should certainly consider obtaining it. Intensive care units will find the book useful. It is not, nor is it intended to be, a substitute for critical reading of original journals.

J. F. Bion

A History of Longworth Scientific Instrument Co. Ltd, 1st Edn Sir Anthony Jephcott. Published by Regency Press Ltd, London and New York. Pp. 202, indexed; illustrated Price £9.50

This book is an account of the development of this instrument makers from their early days to becoming part of a large national firm It is intriguing to see the names of the early partners and employees of the firm, many of whom later developed their own companies. The book shows the involvement of the company with members of the Nuffield Department of Anaesthetics at Oxford and the collaboration which occurred.

There is an emphasis in the book on export sales development of this company and details of many of these trips are described. It is of interest to read how it was possible for a company making anaesthetic apparatus to start from scratch at this time and it is acknowledged that the company made pieces of equipment other than anaesthetic apparatus. It is surprising how what now seems to be a small production of instruments such as laryngoscopes enabled the firm to survive and develop.

This is a book for the anaesthetic and industrial historian. It explains the inter-relationship between several firms and will be a valuable addition to a book-shelf

I. McLellan

Anyone Can Intubate. By C. E Whitten. Published by Medical Arts Press, San Diego, California. Pp. 150; indexed; illustrated. Price US $15.

The sub-title, "A practical, step-by-step guide for health professionals" reveals the intent of the author who, with appropriate enthusiasm, leads her reader through the skills of tracheal intubation The book is illustrated profusely with line drawings, attributed (by inference) to the author's husband and publisher These are exceptionally clear and, with few exceptions, accurate

The literary style is chatty and engaging, while retaining the authority of an experienced professional. The reader should be prepared for North American phrases such as "(the tongue) will mound up like Jello-O", "topicalization with lidocaine", and "the Mac blade"; the somewhat obscure, "the hose follows the nose" and the disarmingly profound, "active suction is wonderful"

Dr Whitten takes us through well illustrated airway anatomy, equipment, techniques and complications. She includes a sensible discussion on general airway management and basic ventilation leading eventually to the handling of the crisis situation by needle crico–thyrotomy She covers nasal and paediatric intubation, the recognition of anticipated intubation problems and tube misplacement. The sections on common errors and difficult intubations are most valuable for the trainee. The line drawings are well placed within the text and are a prime asset of the book.

Inevitably, a first edition has inaccuracies. There are some minor anatomical errors: "the interarytenoid muscles adduct the cords", "xiphoid or breast bone". The text refers to the laryngoscope blade in the midline while the supporting illustrations show the blade well to the left. On page 18 the author states she uses the largest tube possible, yet on page 41 she suggests a 7.5–8 (? internal diameter) for a man.

The bold title, *Anyone Can Intubate*, is seductively positive and more encouraging to the tyro than a more moderate "Learning to Intubate", but Dr Whitten is a punchy author and states, "If you believe you can intubate, you will" which takes enthusiasm to the brink of evangelism—indeed the concept of intubation failure does not truly arise until page 136.

However, this is a superb handbook for those needing to acquire the skills of tracheal intubation and I shall certainly include it in our basic instruction system for medical undergraduates to supplement the intubation training model and audio–visual programme.

T H. Howells

Perspectives in Critical Care Medicine. Edited by F. B Cerra. Published by Quality Medical Publishing Inc., St Louis USA Pp 183; indexed· illustrated Price U.S. $145.

Perspectives in Critical Care Medicine is a new, twice yearly, American publication. The declared aim of the editorial board is to provide a forum for both clinicians and basic scientists to expound and compare their ideas and experiences. The intended readership includes all health care professionals involved in intensive care medicine. The type of subject material covered in this first issue appears, however, to be aimed predominantly at the clinician

Each chapter has a different theme or perspective such as New Technology, Complications, Recent Developments, Ethics, etc Presumably this format will be repeated in subsequent issues Although the quality of each contribution varies and some are of marginal relevance, there are many outstanding features.

The first chapter is a detailed account of the Multiple Organ Failure Syndrome (MOFS). This begins with a description of the various clinical patterns of MOFS followed by discussion of the microbiology, metabolism and pathogenesis. It concludes by examining the current therapeutic options that are available. Standard recommendations are made, with brief mention of those areas in which well established management strategies are being challenged, for example mucosal cytoprotection to control stress ulceration instead of H_2-receptor antagonists; control of enteric flora with selective parenteral/enteral antisepsis regimens.

An internationally renowned panel discuss the importance, identification and management of perfusion deficits in the next chapter, entitled Expert Exchange This amounts to an interesting conversation in which there is an overall consensus of opinion. This is followed by the New Technology section which describes two methods of non-invasive cardiac output measurement with a balanced assessment of Doppler Echocardiography and Thoracic Electrical Bioimpedance.

The Clinical and Therapeutic Significance of Lactic Acidosis is an outstanding contribution. A clear account of the biochemistry of lactate metabolism (a subject covered inadequately by many biochemistry texts) is followed by an explanation of the classification of lactic acidosis into Type A (low flow, ischaemic acidosis) and Type B (metabolic, septic acidosis). This is used to rationalize their different management strategies. The chapter on Recent Developments is concerned principally with nutrition and hypermetabolism Much information from earlier chapters is repeated but there is a useful, comprehensive, and up to date reference section on the subject.

The multidisciplinary nature of intensive care medicine necessitates collation of information on new developments from a variety of sources. The inherent obsolescence of the textbook and the tendency for any important communications to be reported in any number of widely differing specialist journals has resulted in an increasing need for "state-of-the-art" literature. Such publications have gained a well deserved popularity and *Perspectives in Critical Care Medicine* is an addition which goes some way to fulfilling this need. The first issue will be of considerable interest to those who need to be well informed about developments in the metabolic aspects of acute illness, a subject of increasing importance in many ITUs. The quality of paper, print and binding are superb. The very high price does include the cost of two hard-bound volumes, together with 10 issues of a monthly newsletter. Nevertheless, the price may limit purchase to libraries.

D A. B. Turner

Current Practice in Anesthesiology, 1st Edn. Edited by M. Rogers. Published (1988) by B. C. Decker, Inc., Philadelphia. Pp. 328, indexed; illustrated.

The purpose of Mark Rogers, of the Johns Hopkins School of Medicine, Baltimore, in editing *Current Practice in Anesthesiology*, was to produce a book of "short and direct" chapters giving the reader "an insight into practical aspects of anesthesia" Each chapter is written by an expert in the field, and the editor has asked the authors to give their personal views and not to produce "balanced statements designed to offend no one." This approach has been very successful, and has produced an excellent and refreshing textbook.

The book covers most aspects of modern anaesthetic practice, including pain management and intensive care. Each chapter comprises approximately 2000–3000 words and there are very few figures. However, there are many useful tables and the book is well indexed.

The initial worry to the British reader is that the American approach to anaesthesia is often far removed from typical British practice; indeed, every author except one practises in the U.S.A. However, this is not a major problem and only nine of the 79 chapters suffer from this, in particular those concerned with obstetric anaesthesia. The quality of the chapters is also consistently good. I rated 75 % of the chapters as very good or excellent. The monographs on preoperative biochemical screening, cyanotic heart disease, hepatic portal shunting, pancreatic disease, neonatal monitoring and all the chapters on pain therapy were particularly good

The F.C Anaes. (part III) candidate would benefit considerably from perusal of this book. In general, it is clear, precise and well written. Many chapters would provide excellent outlines for essay questions. All anaesthetists would find it extremely useful on occasions, and every departmental library would benefit from its presence.

D. Rowbotham

"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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EDITORIAL

THE SAFETY OF NEW DRUGS

The introduction of a new drug into anaesthetic practice may generally be regarded as beneficial: to the anaesthetist who hopes that old techniques may be improved or new ones developed, to the pharmaceutical company which hopes to expand its business and make a profit for its shareholders, and to the patient who hopes that his prospects for surviving the hazards of surgery may be improved.

Before the drug can be offered for sale, the company must obtain a product licence from the statutory Licensing Authority. In the case of human medicines this is the Minister for Health, advised by the Committee on Safety of Medicines. The application for a such a licence is based on an exhaustive submission which demonstrates that the new product is:

exactly what it says it is (i.e. the chemical structure can be proved, and a reliable synthetic pathway demonstrated),

of satisfactory purity, such that it is not contaminated by reagent residues or unwanted synthetic products, especially those which might have some toxic or pharmacological effects,

free from significant toxic effects in at least two species of laboratory animals,

pharmacologically effective and free from significant adverse effects in laboratory animals,

pharmacologically effective and therapeutically beneficial in man,

free from hazardous adverse effects in man, when used according to the manufacturer's recommendations. This requires evidence of a large database containing records of all adverse effects, obtained during the clinical trial stages.

Such applications are examined by the Committee on Safety of Medicines (CSM) and its two specialist subcommittees: Chemistry and Pharmacy (CPS) and Safety, Efficacy and Adverse reactions (SEAR). The procedures, which include a complex appeals machinery, may be quite protracted, and generally continue until the Committee is persuaded that its rigorous criteria have been satisfied.

Based upon a successful submission, the company must publish a Data Sheet, which sets out the range of licensed applications for the drug, the recommended methods of administration and dosage, relative and absolute contraindications, and possible adverse effects. On obtaining a product licence the Company must, under the provisions of the Medicines Act (1968), make the data sheet freely available to prescribers. All such data sheets are published regularly in a "Data Sheet Compendium" by the Association of the British Pharmaceutical Industry (ABPI).

Quite frequently, licences for entirely new products are limited in scope. Prescribers must be well aware of the range of licensed applications for new drugs, because the manufacturer's liability is limited to usage within those terms. For instance, Diprivan (propofol) is recommended:

"*...for induction and maintenance of general anaesthesia for surgical procedures which generally do not exceed one hour in duration*".

The data sheet states quite clearly:

"*...Experience in procedures lasting more than one hour is limited.*"

Then, in a later paragraph:

"*...At this stage there is no experience of Diprivan in children or in mothers who are breast feeding*".

If, then, a clinician decides to anaesthetize a 4-yr-old patient for a free tissue graft transfer procedure expected to take at least 6 h using a continuous infusion of propofol as the sole agent, but discovers that recovery is not as rapid as he had hoped, he could not legitimately complain that the data sheet had failed to warn him of this possibility.

As experience with a new drug increases, and the scope of clinical trials extends to special groups of patients (such as those at the extremes of age, and those suffering from particular diseases), the manufacturer may submit further evidence to the CSM in order to extend the scope of the product licence. Thus we find that the data sheet for the long-established opioid Operidine (phenoperidine) suggests that it may be used both during anaesthesia and in the intensive care unit, where the indication is stated to be:

"*...as a respiratory depressant/analgesic in patients requiring prolonged assisted ventilation in intensive care units*".

By contrast, the much newer opioid Rapifen (alfentanil) is stated by the same manufacturer to be more restricted in use:

"*...a potent, narcotic analgesic with a very rapid and short-lived action. This makes it especially suitable for use as an adjunct to anaesthesia...*"

"*...may also be administered to ventilated patients undergoing longer operative procedures...*"

—but no mention of intensive care. This does not imply that alfentanil is ineffective in this role; quite the reverse. It is simply that the manufacturer has not yet submitted sufficient evidence to satisfy the CSM that alfentanil is both effective and safe for prolonged administration to critically ill patients.

As already stated, the submission for a product licence includes a substantial safety database, which should give a good indication as to the nature and severity of common adverse effects. However, there are two principal limitations. First, the database is compiled from information gained from highly structured clinical trials. As such trials are designed to demonstrate new virtues or throw light upon specific problems, they do not always have much in common with routine clinical practice. Thus we may see adverse effects appearing more or less frequently, and new side-effects may emerge. Second, the value of a new drug may eventually rest upon the incidence of unusual or even rare adverse effects; the continuing debate as to the clinical usefulness of halothane is a good example. The incidence of unusual adverse drug reactions (ADR) cannot be established from a safety database containing only a few hundred clinical records, and can only emerge as a result of closely monitored clinical use in a large number of patients.

Through its Safety, Efficacy and Adverse Reactions subcommittee (SEAR), the CSM monitors closely the ADR associated with each new drug. All new products are marked in the *Data Sheet Compendium* and *MIMS Monthly Index of Medical Specialties* with an inverted black triangle. This indicates that **all** ADR, however trivial, should be reported to the Committee. These reports are entered into the CSM's *Adverse Reaction Register* which is, in fact, a large computer database. At monthly intervals, all additions to the database are considered by the Adverse Reactions Group of SEAR (ARGUS).

In addition, all reports from anaesthetists are reviewed by the Joint Working Party. By such close monitoring, it is expected that unsuspected ADR will be detected in the shortest possible time. Currently, "black triangle" products of direct interest to anaesthetists include Diprivan (propofol), Nalorex (naltrexone) and Anexate (flumazenil).

It is hoped that the new "Anaesthetic Yellow Card", designed by a joint working party of the College of Anaesthetists, the Association of Anaesthetists and the Committee on Safety of Medicines and now generally available, will facilitate the reporting of Adverse Drug Reactions occurring in anaesthetic practice. These have already been circulated widely, and further supplies can be obtained from:

The Committee on Safety of Medicines
Market Towers,
1, Nine Elms Lane,
London SW8 5NQ

or: call CSM freephone.

The present CSM spontaneous reporting scheme is an effective means of detecting infrequent ADR, but because there is no measure of the number of patients treated it does not give any reliable indication of incidence. Measures of incidence are of the utmost importance, as they may establish clinical preferences on a correct basis, rather than the time-honoured "trial by personal experience" which leads us all to have different perceptions of drugs according to our individual observations.

The true incidence of ADR can be assessed only by large-scale surveillance of both usage and occurrence. In this issue we publish two coordinated surveillance studies of atracurium, which report on data gathered in the U.S.A. [1] and Great Britain [2]. The American database contains data from 1013 patients given atracurium and 851 given other neuromuscular blocking drugs, while the British database contains records of 477 patients given atracurium and 484 given vecuronium. As both studies used identical criteria devised by the Boston Collaborative Drug Surveillance Program, it is possible to make realistic estimates of the relative incidences of the various adverse effects associated with neuromuscular blockers.

The results may surprise readers, and will oblige many, including the author, to revise their perceptions of atracurium. Contrary to expectation [3], the incidence of histamine-related side-effects associated with atracurium are shown to be no more common than with other myoneural blockers. In the British study, "histamine-related" side-effects, such as rash or wheezing, occurred in only 1% and 0.4%, respectively, of atracurium patients, compared with 0.4% and 0.8% of patients given vecuronium. Among American patients given atracurium, only 0.3% developed rash and 1.5% wheezed, compared with 0.1% and 1.8% given other blocking drugs. Possibly histamine-mediated hypotension was equally uncommon in all patients in both studies.

In terms of overall safety, 86.7% of atracurium administrations were entirely uneventful, compared with 87.5% with other drugs in the U.S.A. The comparable figures from the British study were 71% and 60%, respectively. Neither study demonstrates any consistent difference between atracurium and other drugs in the same class.

To reassure those who may regard a 20.2% overall incidence of "possibly drug-related adverse events" as disturbingly high, it must be emphasized that only 3.6% were categorized as "major". Furthermore, this incidence represents the sum of all possible adverse effects from ALL the drugs used in relaxant anaesthesia, and necessarily includes a host of physiological responses to surgical events, which very often cannot be distinguished from true drug-related effects.

These results should be considered alongside those from an even larger study carried out in Australia and reported recently in this Journal [4]. Atracurium was given to 1845 patients and alcuronium to 1420. Most patients were allocated their drug by random selection, but a number of renal failure patients were given atracurium selectively. Notwithstanding that, the two groups were very similar, with closely matched ages, weights, sex distribution and type of surgery. The incidence of atopy was similar in both groups (14.2% *v.* 14.3%). The only notable difference was in the greater proportion of ASA III–V patients given atracurium (21.6% *v.* 11.5%).

In common with the Boston Collaborative Studies, the Australian results were surprising to many, and confounded a long-standing Antipodean preference for alcuronium as the non-depolarizing neuromuscular blocker of choice. Instead of confirming this view, the results show convincingly that, while atracurium causes a higher incidence of local skin reactions (2.5% *v.* 1.5%), the incidence of hypotension was *lower* (3.4% *v.* 13.7%). Of even greater clinical significance, only one patient developed severe hypotension (defined as > 50% decrease in systolic pressure) after atracurium, compared with 11 patients after alcuronium. Overall, the incidences of "possible or probable" ADR were 10.1% for atracurium and 17.9% for alcuronium.

The combined database of 6106 patients enables the incidence of quite unusual events to be estimated. Of course, it is possible that even rarer events remain undetected, so that an even larger database will be needed before we can be quite sure that they do not. Nevertheless, taken together these large studies convey a clear and important message to clinical anaesthetists: there is no foundation whatever for any lingering suspicion that atracurium causes adverse reactions more frequently than other neuromuscular blocking drugs.

It is hoped and expected that, in future, all new drugs will be subjected to such searching analysis. Quite apart from any other reason, it is only by such means that their superiority (or otherwise) over those already available can really be demonstrated.

C. J. Hull

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ATRACURIUM—A POST-MARKETING SURVEILLANCE STUDY: METHODS AND U.S. EXPERIENCE

H. JICK, E. B. ANDREWS, H. H. TILSON, M. PFANSCHMIDT, C. BRANCHE, A. M. WALKER AND D. H. LAWSON

SUMMARY

Two companion post-marketing studies have evaluated the frequency of adverse events amongst patients receiving atracurium. In this first report, we describe the study methods used in both centres and the findings of the study conducted at the Group Health Co-operative of Puget Sound, U.S.A. In this study, the frequency of adverse events in 1013 patients receiving atracurium was substantially the same as that in 851 patients receiving other neuromuscular blocking agents. In both groups there were no instances of cardiac arrest, anaphylaxis or death, no adverse effects associated with failure to antagonize neuromuscular block, and no instances of previously unreported types of adverse effects. We conclude that the safety profile of atracurium is similar to that of other neuromuscular blocking agents and that this type of observational study of anaesthetic agents may prove a useful tool for surveillance of new drugs used primarily in hospitals.

Atracurium is a non-depolarizing neuromuscular blocking agent with an intermediate duration of action [1]. Following introduction of this agent in both the U.S.A. and the U.K., a non-interventional, observational study was established to compare the safety of atracurium with that of other neuromuscular blocking agents during general use. The major objective of the study was to compare the frequency of serious events (such as cardiac arrest), and of events related to histamine release (such as anaphylaxis and other forms of shock) with atracurium relative to other neuromuscular blocking drugs, using well established methods. A secondary objective was to describe and compare the occurrence of less serious adverse events as recorded in the clinical charts (operating room, recovery room and ward), such as frequency of problems resulting from failure of antagonism of neuromuscular block.

In the study, 1864 patients at the hospitals of the Group Health Co-operative of Puget Sound (GHC) in Seattle, Washington, and 961 patients at the Royal Infirmary in Glasgow, Scotland, were observed for adverse events following administration of neuromuscular blockers. A total of 1444 patients who received atracurium and 1302 patients who had received other neuromuscular blocking agents were studied. At GHC, patients receiving any neuromuscular blocking agent other than atracurium were included in the comparison group. In the companion study in Scotland, comparison patients received only vecuronium [2]. Because of differences in surgical populations and comparison groups, data from the two sites have been analysed and are presented separately. This report describes the methodology and presents results from the U.S. study. Findings from the Scottish study are described in the accompanying report [3]. Both studies were co-ordinated by the Boston Collaborative Drug Surveillance Program based on methods used previously [4].

This paper is accompanied by Editorial I.

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U.S. STUDY

SUBJECTS AND METHODS

Between September 1985 and July 1986, a nurse monitor trained in data collection identified surgical patients who received atracurium (group A) within a few days of operation. Verification was achieved by several mechanisms: review of surgical logs, inspection of clinical charts and identification of charts of atracurium-exposed patients by anaesthetic staff. At the time when an atracurium patient was identified, the next patient of the same surgical type (e.g. cholecystectomy) at the same site was selected. Following review of the first 6 months' experience, it was determined that this procedure assured similarity between groups in age, sex and ASA class. At the time of patient identification, the monitor was unaware if any outcome under study had occurred.

For all patients, the entire medical record, including anaesthesia and surgical notes, in addition to all other inpatient records, were reviewed and relevant data (demographic data, baseline clinical status, preoperative, surgical and postoperative medications, events during and following surgery) were recorded on standardized forms of a type previously used by the Boston Collaborative Drug Surveillance Program (BCDSP) for the in-hospital monitoring of surgical patients [4–6]. Because of the observational nature of this study, no attempt was made to alter the manner in which information was recorded in the patients' clinical records. Any adverse event recorded in the clinical chart was recorded on the data collection form by the monitor, who also characterized each adverse event as "major" if it was considered life-threatening or required substantial therapeutic intervention. Other events were classified as "minor" unless, in the judgement of the investigators, they disrupted the surgical procedure or subsequent care of the patient. Examples of major events included reintubation, changes in systolic arterial pressure of greater than 40 mm Hg or decreases in diastolic arterial pressure of more than 20 mm Hg. A heart rate of less than 40 beat min^{-1} would be classified as a major event.

In general, the quality of medical records at GHC is high and data are captured and recorded consistently by physicians. It was anticipated that any major event, such as a change in arterial pressure, and any complication requiring intervention would be recorded in the surgical record. In addition, an event extending into the recovery period which was not reported in the surgical record could also be identified from the record of the recovery room period. Moreover, any serious event, which occurred during the operative period and required additional treatment or observation within the 24–48 h period following surgery, was likely to appear in the medical record or discharge summary, or both. The monitor reviewed all the records for each patient and, if necessary, was able to obtain clarification of any outstanding problems directly from the anaesthetist. Given the multiple records used, the quality of those records and the availability of medical staff for clarification of any questions, the likelihood of missing major adverse events through this process of data collection was low.

From in-hospital clinical records, we identified 1013 patients who received atracurium during surgery (group A). In addition, we identified 851 patients who received neuromuscular blocking drugs other than atracurium during surgery (group O). Of the 1013 Group A patients, 353 received atracurium alone and 660 received other neuromuscular blockers in addition to atracurium. The neuromuscular blocking agents which had been used included vecuronium (for 72 patients this was the only neuromuscular blocking drug (NMB) given), pancuronium (the only NMB for 47 patients) dimethyltubocurarine (the only NMB for nine patients), suxamethonium (the only NMB for seven patients) and tubocurarine (the only NMB for three patients). A majority of patients in both groups also received suxamethonium (65% in group A, 82% in group O). The age distributions in groups A and O were similar (mean 48 yr).

The distribution of surgical procedures was similar in the two groups. Among the 36% of surgical procedures that involved the gastrointestinal tract, the most frequent procedures were cholecystectomy (167 (17%) in group A; 131 (15%) in group O) and appendicectomy (91 (9%) in group A; 97 (11%) in group O). Twenty-four percent of procedures involved the genitourinary system; the most frequent were total hysterectomy (117 (12%) in group A; 126 (15%) in group O), followed by bilateral salpingo-oophorectomy (62 (6.1%) in group A; 67 (7.9%) in group O). A further 12% of procedures involved orthopaedic systems. There appeared to be no important differences in the distribution of operations by drug exposure.

Most patients belonged to ASA classes I and II (82% of group A and 83% of group O patients). Duration of surgery was 1–2 h for 842 (45%) of patients, 2–3 h for 497 (27%) and 3 h or more for 262 (14%). There were no important differences in the distribution of duration of surgery by drug exposure.

RESULTS

None of the patients in the study died in the operating room or recovery room. There was no occurrence of cardiac arrest, anaphylaxis or death in either exposure group. Further, there were no records indicating serious failure to antagonize neuromuscular blockade.

Operating room

Of the 1013 subjects in group A, 135 (13%; 95% confidence interval 11–16%) had an adverse event recorded during surgery. Of 851 group O subjects, 106 (13%; 95% confidence interval 10–15%) had an adverse event (table I). Adverse events of "major" severity were recorded in the operating room for 42 (4.1%) of group A and 31 (3.6%) of group O subjects and events of minor severity occurred in 87 (8.6%) of group A and 71 (8.3%) of group O subjects (table II). For both major and minor events, the observed risk differences between groups A and O were within the bands of random error present in the risk estimates.

TABLE I. *Operating room events (major and minor). Number and percentage of patients who experienced each event*

	Group A (n = 1013) Atracurium		Group O (n = 851) Other blockers		Total (n = 1864)
Event	No.	%	No.	%	No.
Labile arterial pressure	35	3.5	26	3.1	61
Hypotension	18	1.8	13	3.1	31
Bronchospasm/wheezing	15	1.5	15	1.8	30
Hypertension	14	1.4	12	1.4	26
Bradycardia	8	0.8	2	0.2	10
Intubation difficulty	7	0.7	3	0.4	10
Arrhythmia	4	0.4	3	0.4	7
Premature ventricular contractions	3	0.3	3	0.4	6
Laryngospasm	3	0.3	2	0.2	5
Rash	3	0.3	1	0.1	4
Respiratory depression	3	0.3	1	0.1	4
Other	41	30.8	33	31.1	74
No. patients with any event	135	13.3	106	12.5	241
95% Confidence interval	11–16		10–15		

TABLE II. *Severity of operating room events. Number and percentage (95% confidence interval) of patients who experienced each event*

	Group A (n = 1013) Atracurium		Group O (n = 851) Other blockers		Total (n = 1864)
Event	No.	%	No.	%	No.
At least one major event	42 (3.1–5.6)	4.1	31 (2.6–5.1)	3.6	73
At least one minor event	87 (7.0–10.5)	8.6	71 (6.7–10.4)	8.3	158
No event	878	86.7	745	87.5	1623
Events of "unknown" or "decided" severity	6	0.6	4	0.5	10

TABLE III. *Categories of major events in the operating room. Number and percentage of patients who experienced each event*

Event	Group A (*n* = 1013) Atracurium No.	Group A %	Group O (*n* = 851) Other blockers No.	Group O %	Total (*n* = 1864) No.
Events possibly related to histamine release					
Hypotension	4	0.4	3	0.4	7
Bronchospasm/wheezing	2	0.2	2	0.2	4
Tachycardia	1	0.1	3	0.4	4
Laryngospasm	2	0 2	1	0 1	3
Multiple events	1	0.1	1	0.1	2
Total	10	1.0	10	1.2	20
Other cardiovascular events					
Hypertension	7	0.7	5	0.6	12
Labile arterial pressure	6	0.6	4	0.5	10
Bradycardia	4	0.4	0	0.1	4
Arrhythmia	3	0 3	1	0.1	4
Premature ventricular contractions	2	0.2	2	0.2	4
Other	2	0.2	1	0.1	3
Multiple events	2	0.2	1	0.1	3
Total	26	2.6	14	1.6	40
Other respiratory events	3	0.3	5	0.5	8
Other events	3	0.3	5	0.5	8
Total patients with major events	42	4.1	31	3.6	73

Major events were grouped according to categories of principal interest (table III). Ten (1.0%) group A patients and 10 (1.2%) group O patients experienced major events which were related possibly to histamine release: hypotension, bronchospasm and tachycardia were the most frequent, and were distributed equally between the two groups. Twenty-six (2.6%) group A patients and 14 (1.6%) group O patients (table III) experienced major cardiovascular events, excluding hypotension and tachycardia, but major respiratory events, other than bronchospasm/wheezing, were infrequent in both groups (0.2% in group A and 0.1% in group O).

To assess the possible contribution of suxamethonium to the occurrence of adverse events, the data for patients in whom there was concomitant use of suxamethonium were analysed separately. A total of 660 patients received suxamethonium and atracurium and 702 patients received suxamethonium and other neuromuscular blockers. No material differences were observed in the frequency or type of major adverse events between these groups. Similarly, when data from subjects who did not receive suxamethonium were analysed separately, there were no differences of any consequence between groups A and O.

The results were reviewed separately by type and duration of surgery as a precaution against the possibility that each factor may have masked an association between atracurium and major adverse events. No differences were evident between the two exposure groups in frequency or type of major adverse event.

Recovery room

There was little difference between groups A and O for recovery room events (table IV). A smaller observed risk for major events in the recovery room among group A patients (3.9% *v* 6.0%) was not compatible with chance ($\chi^2_1 = 4.59$, $P = 0.03$).

Major events in the recovery room were grouped according to categories of principal interest (table V). Eleven (1.1%) group A and 17 (2.0%) group O patients experienced an event related possibly to histamine release. Hypotension was the most frequent event, experienced by nine subjects (0.9%) in group A and 14 (1.6%) in group O.

Among patients with major cardiovascular

TABLE IV. *Severity of recovery room events. Number and percentage (95% confidence interval) of patients who experienced each event. *Relative risk = 0.643 comparing atracurium with other blockers;* $\chi^2 = 4.589$; P = 0.032

Event	Group A (n = 1009) Atracurium No.	%	Group O (n = 849) Other blockers No.	%	Total (n = 1858) No.
At least one major event	39* (2.8–5.1)	3,9	51* (4.6–7.8)	6.0	90
At least one minor event	105 (8.8–12.5)	10.4	96 (9.3–13.6)	11.3	201
No event	865	85.7	700	82.4	1565
Events of "undecided" severity	0		2	0.2	2

TABLE V. *Categories of major events in the recovery room. Number and percentage of patients who experienced each event*

Event	Group A (n = 1009) Atracurium No.	%	Group O (n = 849) Other blockers No.	%	Total (n = 1858) No.
Events possibly related to histamine release					
Hypotension	9	0.9	14	1.6	23
Bronchospasm/wheezing	0		2	0.2	2
Rash	0		1	0.1	1
Tachycardia	1	0.1	0		1
Laryngospasm	1	0.1	0		1
Total	11	1.1	17	2.0	28
Other cardiovascular events					
Hypertension	11	1.1	9	1.1	20
Premature ventricular contractions	0		4	0.5	4
Bigeminy	0		2	0.2	2
Bradycardia	0		1	0.1	1
Labile arterial pressure	1	0.1	0		1
Arrhythmia	0		1	0.1	1
Heart block	1	0.1	0		1
Multiple events	0		1	0.1	1
Total	13	1.3	18	2.1	31
Other respiratory events	11	1.1	10	1.2	21
Other events	4	0.4	6	0.7	10
Total patients with major events	39	3.9	51	6.0	90

events (excluding hypotension and tachycardia), hypertension was most frequent (11 (1.1%) in group A; nine (1.1%) in group O). Premature ventricular contractions occurred in four (0.5%) patients in group O. Overall, there were 13 (1.3%) major cardiovascular events in group A and 18 (2.1%) in group O. Eleven (1.1%) patients in group A and 10 (1.2%) in group O experienced major respiratory events, excluding bronchospasm/wheezing (table V). Respiratory depression was the most frequent of these events, (four (0.4%) in group A; four (0.5%) in group O).

The possible contribution of suxamethonium was analysed in the recovery of these patients, and again there were no important differences.

DISCUSSION

Atracurium has been used widely in the United Kingdom since approval by the Committee on

Safety of Medicines in July 1982 and in the U.S. since approval by the Food and Drug Administration in December 1983. The most common adverse events noted from clinical trials are skin flushing, hypotension and bronchospasm [7,8].

In this U.S. study of 1864 patients who received neuromuscular blocking drugs, few serious adverse events were recorded during surgery or in the recovery room. In particular, there were no instances of cardiac arrest, anaphylaxis or death. Furthermore, there were no episodes of unexpected or previously unreported events, nor were there instances of reported difficulties in antagonism of neuromuscular block.

There were no significant differences in rates of serious adverse events in patients who received atracurium compared with those who did not. This was true for major and minor events, for those possibly related to putative histamine release, and for cardiovascular and respiratory events. However, this method may not have been sensitive to subtle differences in the occurrence of minor events. For example, difficulty in antagonism of neuromuscular block, unless serious or unusual, may not be recorded in the clinical record. Because of possible differences between anaesthetists and surgeons in recording minor events, comparisons between exposure groups of minor events may be less instructive than comparions of major events. Furthermore, such comparisons were not the primary purpose of this study.

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ATRACURIUM—A POST-MARKETING SURVEILLANCE STUDY: U.K. STUDY AND DISCUSSION

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SUMMARY

Two companion post-marketing studies have evaluated the frequency of adverse events amongst patients receiving atracurium. In this second report, we describe the Scottish study and discuss findings in both centres. In this study we compare the frequency of adverse events in 477 patients receiving atracurium with those in 484 patients who received vecuronium. The frequency of reported serious adverse events was low during surgery and in the recovery room. Although the overall incidence of adverse experiences was slightly lower after atracurium, there were no significant difference between the groups in frequency of major adverse events. This type of study is believed to be of value in the future surveillance of new drugs for hospital use.

Following the introduction of atracurium and vecuronium into the U.K. and U.S.A., observational studies were established to assess the safety of atracurium under conditions of general use. The previous paper described the general methods and the findings of the U.S. study. The present report describes the Scottish study, in which adverse events experienced by a group of atracurium recipients were compared with those experienced by a group of vecuronium recipients. In the Seattle study [1], adverse events experienced by a group of atracurium recipients were compared with those experienced by patients receiving any other neuromuscular blocking agent(s). Both studies were co-ordinated by the Boston Collaborative Drug Surveillance Program [2].

U.K. STUDY

The objectives of the present study were to compare the risks of serious adverse experiences associated with use of atracurium and of vecuronium; to detect any unsuspected or severe adverse experiences related to atracurium under conditions of general use; to determine if there were measurable risks of reactions associated with atracurium which could be related to histamine release; to measure the frequency of specific events such as hypertension, hypotension, tachycardia, bradycardia and respiratory depression in recipients of atracurium and vecuronium; and to identify and quantitate the occurrence of any unexpected problems with antagonism of neuromuscular block.

PATIENTS AND METHODS

We studied 961 patients admitted to Glasgow Royal Infirmary between September 1985 and July 1986. They received either atracurium or vecuronium during operation and thereafter a detailed record of all clinical notes and laboratory data was obtained in a standard fashion by a trained nurse monitor (G.P.) using record forms designed and in routine use by the Boston Collaborative Drug Surveillance Program (BCDSP) as described previously [1].

Upon completion, all data were reviewed by one of us (D.H.L.) before being submitted to the BCDSP office for editing, coding and entry on to computer.

This article is accompanied by Editorial I.

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TABLE I. *Principal medications used in the operating theatre*

	Group A (*n* = 477) Atracurium	Group V (*n* = 484) Vecuronium
Nitrous oxide	466	481
Thiopentone	457	477
Halothane	319	310
Neostigmine	300	383
Atropine	244	248
Papaveretum	233	135
Enflurane	138	173

A total of 477 concurrent atracurium recipients were studied (group A) and compared with 484 concurrent vecuronium recipients (group V). The age, sex and racial distributions of these two groups were similar (mean age 53 yr, 49% male, 99% Caucasian). Of the 47% of procedures which involved the gastrointestinal system, cholecystectomy (16%) and repair of inguinal hernia (9.7%) were the most frequent. Genito-urinary operations comprised 14% of the procedures (ligation of varicocele 2.8% and hysterectomy 2.6% were most frequent). A further 12% of procedures involved the vascular system. There were minor differences between groups A and V with regard to the types of surgical operations undertaken; however, these were not related to outcome measurements. The duration of surgery was similar in both groups (average 1.5 h). Distribution of patients by ASA class was similar in the two groups: 24% ASA I; 32% ASA II; 36% ASA III; 8% ASA IV. No patient in either group was ASA V. Additional anaesthetic medications received by patients in each group are shown in table I.

RESULTS

Operating room

Of the 477 subjects in group A, 137 patients (29%, 95% confidence intervals 25–33) experienced a total of 178 adverse events during surgery, compared with 193 patients (40%, 95% confidence intervals 35–44) of the 484 subjects in group V, who experienced a total of 257 adverse events during surgery (table II). Adverse events of major severity were recorded in the operating room for 12 subjects in group A (2.5%) and 16 in group V (3.3%) (table III). The difference between the groups with respect to major events was not explained by concurrent use of suxamethonium. Overall, six patients in group A and five in group V experienced events which were related possibly to histamine release. No patient experienced a cardiac arrest during operation, nor were there any instances of anaphylaxis or major respiratory events occurring in the operating theatre.

Adverse events of minor severity were recorded in the operating room for 125 subjects in group A (26%, 95% confidence intervals 22–30) and 177 (37%, 95% confidence intervals 32–41) in group V.

Totals of 340 patients in group A (71%) and

TABLE II. *Events recorded in the operating theatre. Number and percentage of patients who experienced each event*

	Group A (*n* = 477)		Group V (*n* = 484)	
Event	No.	%	No.	%
Hypotension	72	15.0	93	19.0
Bradycardia	57	12.0	86	18.0
Arrhythmia	6	1.3	11	2.3
Urinary output decreased	9	1.9	6	1.2
Hypertension	3	0.6	12	2.5
Tachycardia	2	0.4	9	1.9
Bigeminy	4	0.8	4	0.8
Respiratory depression	2	0.4	6	1.2
Rash	5	1.0	2	0.4
Haemorrhage	6	1.3	1	0.2
Nodal rhythm	3	0.6	4	0.8
Bronchospasm/wheezing	2	0.4	4	0.8
Other	7	1.5	19	3.9
Any event	137	29.0	193	40.0

TABLE III. *Major events in the operating theatre.* * *Events related possibly to histamine release*

Major event	Group A ($n = 477$) Atracurium	Group V ($n = 484$) Vecuronium
Hypotension/bradycardia*	1	2
Hypotension/bradycardia/arrhythmia*	1	0
Hypotension/haemorrhage*	1	0
Hypotension*	3	1
Sinus arrest*	0	2
Hypertension	0	3
Bradycardia	2	4
Arrhythmia	1	0
Bigeminy	0	1
Haemorrhage	3	1
Aspiration	0	1
Pulmonary complications	0	1
Total	12 (2.5%)	16 (3.3%)

291 in group V (60%) had no reported events in the operating room.

There were no recorded instances of difficulty in antagonism of neuromuscular block.

Recovery room

We monitored 431 atracurium recipients (90%) and 451 vecuronium recipients (93%) in the recovery room. Of these, 101 in group A (23%) and 100 in group V (22%) experienced an adverse event in the recovery room, but only eight in group A (1.9%) and seven in group V (1.6%) were major (table IV). In two patients the major event could have been related to histamine release, one (tachycardia) occurred in an atracurium recipient and one (hypotension) occurred in a vecuronium recipient. Other major events included hypertension, arrhythmia and respiratory depression. All were distributed equally with respect to neuromuscular blocking therapy. There were no differences in the frequency of major events between the groups in relation to concurrent use of suxamethonium.

Overall, there were 93 minor events in the recovery room in group A patients (22%) and 93 in group V (21%).

TABLE IV. *Major events in the recovery room.* * *Events related possibly to histamine release*

Major event	Group A ($n = 431$) Atracurium	Group V ($n = 451$) Vecuronium
Hypotension*	0	1
Tachycardia*	1	0
Hypertension	2	4
Bradycardia	2	0
Arrhythmia/acute left ventricular failure	1	0
Arrhythmia	1	0
Respiratory depression	0	1
Haematoma	1	0
Hypokalaemia	0	1
Total	8 (1.9%)	7 (1.6%)

DISCUSSION

In this study of 961 consecutive surgical patients who received treatment with the neuromuscular blocking agents atracurium and vecuronium, the frequency of reported serious adverse events occurring during surgery or in the recovery room was low. Small differences were observed in the overall occurrence of adverse experiences, fewer atracurium than vecuronium patients experiencing adverse events. However, no significant differences were observed for major events. For minor events, the differences were explained largely by the lower proportion of atracurium recipients experiencing hypotension and bradycardia. Because of variability between anaesthetists in their criteria for assessing such minor events, it would be inappropriate to draw inferences on comparative drug safety from these relatively small differences. There were no unexpected or previously unreported events which may have been drug-induced, and no significant difficulty in antagonizing neuromuscular block at the end of operation.

The frequency of major events recorded in the operating and recovery rooms in both the Seattle and Glasgow studies of atracurium recipients was similar to those of previous reports from the Boston Collaborative Drug Surveillance Program using the same methodology [2,3]. In these studies, major adverse events were reported in fewer than 5% of patients in the operating room.

Concern has been expressed previously on histamine release following use of most induction agents, neuromuscular blocking drugs and opioids [4]. This is associated usually with minor cutaneous effects, flushing or minor bronchospasm, which may be unrecorded in our studies. The role of histamine release in severe reactions is less clear [5] and is often difficult to elucidate, as many potent drugs may release histamine (e.g. morphine, tubocurarine, atracurium, vecuronium). Moreover, the relationship between histamine release and hypotension has been questioned [6]. We may infer from our study only that there were no material differences between atracurium and other neuromuscular blockers (including vecuronium) regarding the frequency of relatively common major or minor events in the operating room or recovery room, whether or not these events have been related to histamine release in the past. Although some minor events such as transient skin rash or mild bronchospasm may have gone unrecorded, these would have been of such minimal significance as to require no remedial action.

The absence of a significant difference in cardiovascular events between the atracurium and comparison groups in the U.S. study was corroborated in the U.K. study; however, in the latter, patients in the vecuronium group experienced more cardiovascular events than the atracurium group.

In a large study of 112000 anaesthetics in a teaching hospital between 1975 and 1983, Cohen and her colleagues [7] reported that minor complications attributed to anaesthesia occurred in 8.9% of anaesthetics and major complications in 0.4%. However, this study recorded only major events which were thought by anaesthetists to be complications of anaesthetic procedures and thus is more in keeping with an augmented spontaneous reporting scheme, as distinct from the present study, which recorded all adverse events experienced in surgery and during recovery, regardless of whether or not they were thought to be "adverse reactions" to any of the many drugs used during anaesthesia. Thus we avoided attribution of an individual event to a specific agent in an individual case. In such an epidemiological approach, through unbiased counting of adverse events and comparison across exposure groups, any important side effects associated with the medications under study may be expected to emerge if they occur at higher frequencies with one of the comparison drugs. In the present studies, the size of the population reviewed is sufficient to detect a relative risk of 10 for events occurring with a frequency of one in 500 patients in the comparison group and a relative risk of 3 for events occurring in one of 100 patients in the comparison group (alpha = 0.05, power > 80%).

The adverse events experienced in these two studies of a total of 2825 patients were both manageable and reversible without sequelae. Neither atracurium nor vecuronium was associated with qualitative or quantitative increases in the risk of adverse events in surgery or during the recovery phase over that experienced by patients who received other neuromuscular blocking agents. However, a difference in the rates of rarer but possibly important side effects, if they exist, could not be detected in studies of these limited sizes.

We recommend that this type of observational study of drugs, as they are used in standard clinical practice, should be undertaken more frequently as part of the development of a post-marketing surveillance profile of new chemical entities used primarily in hospital environments.

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EFFECT OF NALBUPHINE HYDROCHLORIDE ON THE VENTILATORY AND OCCLUSION PRESSURE RESPONSES TO CARBON DIOXIDE IN VOLUNTEERS

G. C. PUGH, D. T. BROWN AND G. B. DRUMMOND

SUMMARY

We studied the effect of nalbuphine on the ventilatory and occlusion pressure reponses to carbon dioxide rebreathing in six healthy male volunteers (mean age 25.5 yr) in a single-blind laboratory study. On four separate days volunteers were assigned randomly to receive either placebo (0.9% sodium chloride) or three i.v. doses of nalbuphine (15, 30 and 60 mg 70 kg^{-1}), followed 90 min later by naloxone 0.4 mg 70 kg^{-1}. Duplicate rebreathing tests were performed and the mean intercept at PE'_{CO_2} 7 kPa and the slopes of the linear relationship between inspiratory minute ventilation ($\dot{V}_I$) or occlusion pressure ($P_{0.1}$) with PE'_{CO_2} were measured. Nalbuphine significantly decreased the mean intercept of the $\dot{V}_I$ ($P < 0.01$) and $P_{0.1}$ ($P < 0.05$) responses, but caused no changes in the slopes. No significant difference between the doses was noted, suggesting that an Effect maximum (E'max) for respiratory depression was reached with a dose of approximately 15 mg 70 kg^{-1}. Naloxone was less effective in antagonizing the depression in $\dot{V}_I$ at the higher dose of nalbuphine. Similar $P_{0.1}$ values were associated with the same inspiratory flow rate (1 litre s^{-1}) before and after drug treatment, suggesting that nalbuphine acts centrally to depress ventilation. Sedation increased significantly following each dose of nalbuphine ($P < 0.001$). No demonstrable difference between the doses was shown, suggesting an Effect maximum (E'max) for sedation was reached at about 15 mg 70 kg^{-1}. Administration of nalbuphine was associated with pain at the injection site, dizziness, dreaming, nausea and vomiting. Cardiovascular stability was maintained in all subjects.

Opioid analgesics decrease respiratory responses to carbon dioxide. Pure agonists, such as morphine, depress ventilation in a dose-related manner [1, 2] while those with partial antagonist activity such as nalorphine [3], pentazocine [4], butorphanol [5] and nalbuphine [6] show an Effect maximum (*E*′max) for respiratory depression at small clinical doses.

Respiratory depression by anaesthetics and opioids has been attributed to other mechanisms such as altered mechanical factors in the respiratory system [7, 8] in addition to a reduction in central neural drive. Discrimination between these two mechanisms may be determined by measuring airway occlusion pressure ($P_{0.1}$) which allows a more direct index of neural activity and is less dependent on changes in impedance of the respiratory system [9].

The present study was designed to measure both ventilation ($\dot{V}_I$) and $P_{0.1}$ responses to carbon dioxide and to assess the relative contribution of central and mechanical factors in the ventilatory depression associated with clinical doses [10] of nalbuphine. We also studied the ease of antagonism of the ventilatory depression with naloxone.

SUBJECTS AND METHODS

Six healthy non-smoking male volunteers aged 19–34 yr gave written consent for the study, which was approved by the local Ethics Committee. No subject was taking medication or had taken drinks containing caffeine for 12 h before the study. Each subject was studied at the same

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time of day, 2–3 h after a non-fatty breakfast. Vital capacity and forced expiratory volume in 1 s were measured with the subject standing. A slow i.v. infusion of sodium chloride 150 mmol litre^{-1} was started.

No subject had previous experience of the rebreathing method. A practice rebreathing was allowed to familiarize each subject with the apparatus. At the same time of day, at least 4 days apart, subjects received either placebo (0.9% sodium chloride) or three randomly assigned doses of nalbuphine (15, 30 and 60 mg 70 kg^{-1}), administered i.v. over 5 min. (These doses are referred to subsequently as 15-, 30- and 60-mg doses.) Naloxone 0.4 mg 70 kg^{-1} was given i.v. 90 min after each dose of nalbuphine. The subject was unware of the dose or the timing of the drugs administered.

Duplicate rebreathing tests were performed with the subject in the lying and then the sitting position. A standard sitting position was achieved using a padded polystyrene back-rest moulded for each subject. Rebreathing was commenced at -30 min (control), 30 min (30 min after placebo or nalbuphine), 90 min (immediately after i.v. naloxone 0.4 mg 70 kg^{-1}) and 150 min (1 h after naloxone). Each rebreathing test was completed in approximately 3–4 min. Sufficient time (usually 2–3 min) was allowed for $P\text{E}'_{CO_2}$ to return to the pre-rebreathing value before the next rebreathing test was started.

The ventilatory response to carbon dioxide was determined by a modified Read method [11]. Subjects wore a noseclip and rebreathed from a 5 litre bag filled with 6% carbon dioxide in oxygen, using a mouth piece via a large bore three-way tap and an open occlusion valve. The rebreathing bag was surrounded by a rigid container connected to a spirometer (Wedge, Med Science 570). Volume calibration of the spirometer was achieved electronically. The three-way tap allowed subjects either to breathe air or to rebreathe from the bag. The inspiratory and expiratory resistances of the apparatus were 0.02 kPa litre^{-1} s at a flow rate of 30 litre s^{-1}. Gas was sampled close to the mouth and returned to the bag. The gas was analysed with a rapid response carbon dioxide analyser (Engstrom Eliza) to allow a continuous record of carbon dioxide at the mouth and thus measurement of end-tidal partial pressure ($P\text{E}'_{CO_2}$). Two mixtures of carbon dioxide (6.0 and 8.5%) in nitrogen were used to calibrate the carbon dioxide analyser.

Airway pressure (Paw), carbon dioxide concentration and inspired and expired volume and flow signals were recorded on a six-channel UV recorder (Bell and Howell 5-137). Measurements were taken from the recording with a digitizer (resolution to 0.1 mm; Terminal Display System Limited LC-12) linked to a microcomputer (BBC B plus). Measurements were taken from the rebreathing records after the increase in $P\text{E}'_{CO_2}$ has become linear with time. Measurements of $T\text{I}$, $T\text{E}$, $V\text{T}$ and $P\text{E}'_{CO_2}$ were taken from the individual breaths on the trace preceding airway occlusion. $T\text{I}$ and $T\text{E}$ were measured from the flow record. $\dot{V}\text{I}$ was calculated as $V\text{T} \times 60/(T\text{I}+T\text{E})$ and was not corrected to BTPS. Mean inspiratory flow rate was calculated as $V\text{T}/T\text{I}$.

A pneumatic device was used to hold the occlusion valve open during normal inspiration. At random times during rebreathing and without the knowledge of the subject, it was inactivated during expiration so that inspiratory flow was prevented during the next inspiratory effort. The valve was reopened 200–300 ms later. The subatmospheric Paw developed during the occluded inspiratory attempt was measured by a transducer (calibrated with a water manometer) connected to the mouthpiece (Furness Controls Ltd, FCO 40: range ± 250 mm H_2O) and recorded on an FM tape recorder (Thermionic). The Paw signals were later replayed from the tape recording to the UV recorder at a speed of 10 cm s^{-1} to permit the measurement of $P_{0.1}$ 100 ms after Paw had become less than -0.1 kPa, rather than after the pressure became less than atmospheric [12]. During rebreathing, airway occlusions (six to 10) were performed at random intervals separated by six to 10 normal breaths.

Serum concentrations of nalbuphine were measured by high pressure liquid chromatography to confirm that satisfactory concentrations were achieved at the time the ventilatory studies were performed. Venous blood samples were taken at 60 min before and 30 and 60 min after administration of the placebo or nalbuphine. The assay was sensitive to 1 ng ml^{-1} and specific for nalbuphine, with no cross reaction with metabolites. The coefficient of variation was $< 2\%$ for nalbuphine concentrations > 6 ng ml^{-1}. Nalbuphine concentrations in serum and plasma are identical (Aitkenhead AR and Achola KJ, personal communication) and in this paper the term "plasma" has been used to describe the serum concentration.

Sedation was assessed with a linear analogue scale (horizontal 10-cm scale from alert to drowsy) at 30 min before and 30 and 150 min after administration of nalbuphine. Systolic and diastolic arterial pressures and heart rate were recorded at 15-min intervals (Dinamap). Other side effects of nalbuphine administration were recorded.

The change in $\dot{V}\text{I}$ with increasing $P\text{E}'_{CO_2}$ was calculated by least squares linear regression. The relationship was assessed both from $\dot{V}\text{I}$ when $P\text{E}'_{CO_2}$ was 7 kPa and from the slope of the relationship ($\dot{V}\text{I}/P\text{E}'_{CO_2}$). Although the relationship between $P_{0.1}$ and $P\text{E}'_{CO_2}$ was not linear, the relationship between $\log_e P_{0.1}$ and $P\text{E}'_{CO_2}$ was, and consequently linear regression relationships between $\log_e P_{0.1}$ and $P\text{E}'_{CO_2}$ were used to characterize the $P_{0.1}$ responses.

In order to assess any change in relationship between $P_{0.1}$ and $V\text{T}/T\text{I}$, the regression relationship between $V\text{T}/T\text{I}$ and $P\text{E}'_{CO_2}$ was used to determine the $P\text{E}'_{CO_2}$ associated with a $V\text{T}/T\text{I}$ of 1 litre s^{-1}. The relationship between $\log_e P_{0.1}$ and $P\text{E}'_{CO_2}$ was used to estimate the $P_{0.1}$ value at this $P\text{E}'_{CO_2}$. This value was therefore the $P_{0.1}$ value associated with a $V\text{T}/T\text{I}$ of 1 litre s^{-1}. In this way, $P_{0.1}$ values associated with the same flows, before and after drug administration, were compared. This is more appropriate in the assessment of $P_{0.1}/(V\text{T}/T\text{I})$ relationship than simple comparison of $P_{0.1}$ values at the same $P\text{E}'_{CO_2}$, as the $V\text{T}/T\text{I}$ of a subject at a given $P\text{E}'_{CO_2}$ would be altered by drug administration, and the relationship between $P_{0.1}$ and $V\text{T}/T\text{I}$ may not be assumed to be linear.

Mean values for the duplicate measurements were calculated, and these values were used subsequently in statistical analysis. Because the slopes of responses to carbon dioxide are not distributed normally [13], these values were transformed by taking natural logarithms before statistical analysis. For descriptive purposes, mean values for all subjects, in each position and at each measurement time, were calculated and are illustrated in the figures.

Statistical comparisons of changes in the intercept and in the log slope, before and after each drug administration, before and after administration of naloxone, and immediately after and 1 h after naloxone, were made using a paired *t* test. Comparison between the effects of different doses of nalbuphine was made using analysis of variance. Sedation scores were compared before and after drug administration with the Wilcoxon test, and between doses with the Mann–Whitney *U* test [14].

RESULTS

Details of the subjects are given in table I. All subjects successfully completed the study. However, immediately following nalbuphine administration, severe nausea prevented two subjects from completing one of their rebreathing tests in the sitting position.

Ventilatory response to carbon dioxide

A greater $\dot{V}\text{I}$ was recorded with the volunteers rebreathing in the sitting position (fig. 1). However, the pattern of change in $\dot{V}\text{I}$ following administration of nalbuphine or naloxone was similar in both positions. The intercepts of the relationship at $P\text{E}'_{CO_2}$ 7 kPa were similar throughout the placebo day and for the control values on each drug day. Following each dose of nalbuphine, the intercept was reduced significantly, but no significant difference between the doses could be shown.

In comparison with the uniform depressant effect of the different doses of nalbuphine, naloxone had different effects in lying and sitting subjects (fig. 1). In lying subjects, naloxone 15 mg and 30 mg significantly increased the intercept, but antagonism was incomplete. In sitting sub-

TABLE I. *Details of subjects studied*

Subject	Age (yr)	Height (cm)	Weight (kg)	FEV/FVC (litre)	Weight (% of ideal)	Expected weight (kg)
AH	19	183	71	4.60/6.50	99	72.6
JM	30	173	68	4.40/6.32	93	73
JH	25	175	67	4.65/7.30	93	72.1
JB	24	173	73	4.60/5.15	108	67.6
TT	34	183	72	5.10/6.50	89	81.2
ST	21	173	70	4.20/4.95	103	67.6

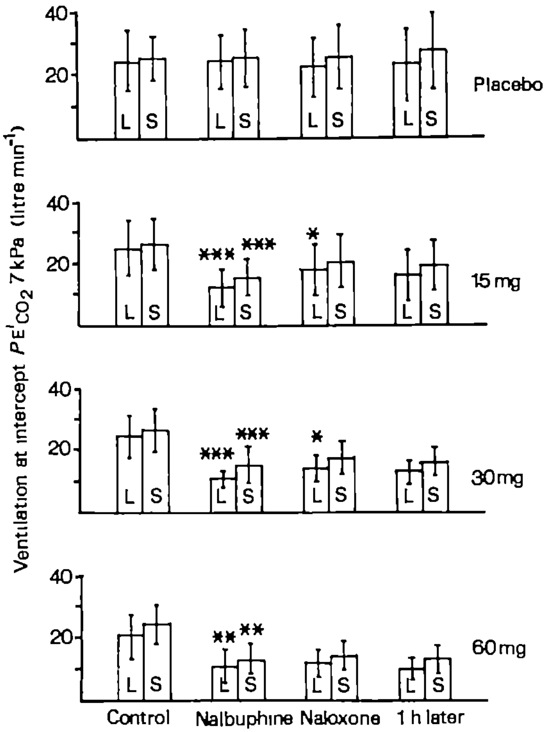

FIG. 1. Mean (SD) intercept at $P\text{E}'_{\text{CO}_2}$ 7 kPa for $\dot{V}\text{I}$ (litre min^{-1}) against $P\text{E}'_{\text{CO}_2}$ (kPa), in the lying (L) and sitting (S) positions for the nalbuphine "treatment days" (placebo; nalbuphine 15, 30 and 60 mg 70 kg^{-1}) at the control time, following nalbuphine, naloxone and 1 h later. $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

jects, the intercept decreased 1 h after naloxone, but the change was not significant.

The log slope of the linear relationship of $\dot{V}\text{I}$ with $P\text{E}'_{\text{CO}_2}$ did not change significantly after administration of either nalbuphine or naloxone except following nalbuphine 30 mg in the sitting position (table II).

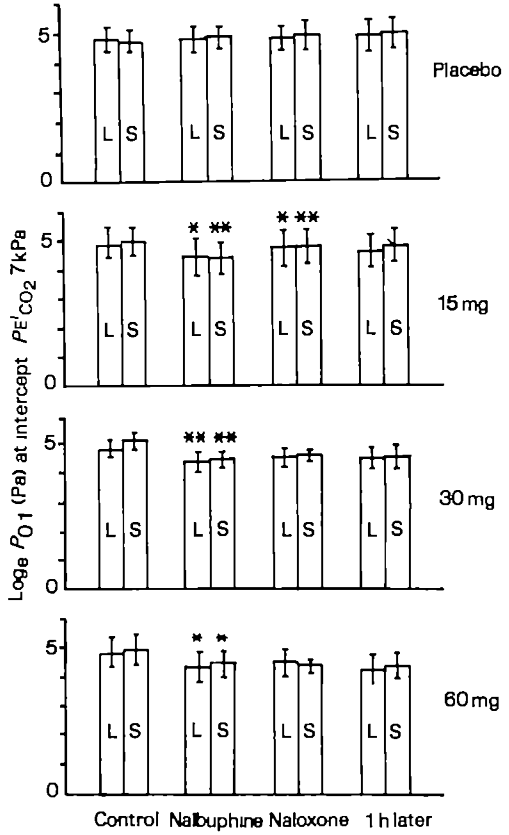

FIG. 2. Mean (SD) intercept at $P\text{E}'_{\text{CO}_2}$ 7 kPa for the log $P_{0.1}$ (Pa) against $P\text{E}'_{\text{CO}_2}$ (kPa), in the lying (L) and sitting (S) positions for the nalbuphine "treatment days" (placebo; nalbuphine 15, 30 and 60 mg 70 kg^{-1}) at the conrol time, following nalbuphine, naloxone and 1 h later. $^*P < 0.05$; $^{**}P < 0.01$.

Occlusion pressures

The intercepts throughout the placebo day and the control values on each drug day were similar (fig. 2). Compared with control, each dose of

TABLE II. *Mean (SD) log slope (litre min^{-1} kPa^{-1}) of the relationship of* $\dot{V}\text{I}$ *(litre min^{-1}) with* $P\text{E}'_{\text{CO}_2}$ *(kPa) in lying and sitting subjects.* $^*P < 0.05$

	Placebo	15 mg	30 mg	60 mg
Lying				
Control	2.96 (0.30)	2.87 (0.28)	2.86 (0.23)	2.82 (0.15)
Nalbuphine	2.81 (0.39)	2.59 (0.46)	2.53 (0.67)	2.47 (0.60)
Naloxone	2.81 (0.40)	2.74 (0.37)	2.74 (0.30)	2.60 (0.20)
1 h later	2.86 (0.37)	2.73 (0.36)	2.61 (0.20)	2.63 (0.24)
Sitting				
Control	2.74 (0.24)	2.92 (0.23)	2.89 (0.23)	2.72 (0.18)
Nalbuphine	2.80 (0.35)	2.70 (0.33)	2.65 (0.36)*	2.69 (0.26)
Naloxone	2.81 (0.33)	2.72 (0.39)	2.68 (0.31)	2.54 (0.22)
1 h later	2.85 (0.36)	2.75 (0.35)	2.66 (0.24)	2.62 (0.24)

TABLE III. *Mean (SD) log slope (Pa kPa^{-1}) of the relationship of log $P_{0.1}$ (Pa) with PE'_{CO_2} (kPa) in lying and sitting subjects.* $*P < 0.05$

	Placebo	15 mg	30 mg	60 mg
Lying				
Control	−0.06 (0.29)	−0.07 (0.16)	−0.09 (0.19)	−0.15 (0.30)
Nalbuphine	−0.05 (0.29)	−0.12 (0.16)	−0.12 (0.32)	−0.06 (0.28)
Naloxone	−0.05 (0.26)	−0.03 (0.27)	0.08 (0.22)	−0.07 (0.22)
1 h later	−0.04 (0.33)	0.04 (0.29)	−0.08 (0.14)	0.09 (0.24)*
Sitting				
Control	−0.21 (0.16)	−0.17 (0.20)	−0.14 (0.28)	−0.31 (0.22)
Nalbuphine	−0.25 (0.17)	−0.12 (0.22)	−0.30 (0.35)	−0.05 (0.21)*
Naloxone	−0.09 (0.23)	0.05 (0.28)	−0.06 (0.17)	0.01 (0.25)
1 h later	−0.12 (0.21)	−0.17 (0.26)*	−0.05 (0.17)	−0.03 (0.35)

TABLE IV. *Values (SD) of $P_{0.1}$ (kPa) predicted from linear regression relationship of log $P_{0.1}$ with PE'_{CO_2} using PE'_{CO_2} values that give a mean inspiratory rate of 1 litre s^{-1} in lying and sitting subjects*

	Placebo	15 mg	30 mg	60 mg
Lying				
Control	0.168 (0.055)	0.183 (0.103)	0.175 (0.085)	0.201 (0.106)
Nalbuphine	0.200 (0.118)	0.314 (0.231)	2.048 (4.460)	8.168 (19.448)
Naloxone	0.222 (0.115)	0.243 (0.115)	0.247 (0.144)	0.241 (0.088)
1 h later	0.204 (0.089)	0.239 (0.134)	0.224 (0.109)	0.261 (0.108)
Sitting				
Control	0.153 (0.064)	0.169 (0.088)	0.166 (0.094)	0.179 (0.095)
Nalbuphine	0.182 (0.092)	0.185 (0.118)	0.190 (0.077)	0.221 (0.099)
Naloxone	0.185 (0.083)	0.243 (0.183)	0.196 (0.095)	0.209 (0.085)
1 h later	0.173 (0.076)	0.214 (0.141)	0.187 (0.124)	0.205 (0.070)

nalbuphine significantly decreased the intercept in the lying and sitting subjects. We could not demonstrate any significant difference in the reduction of $P_{0.1}$ caused by any of the doses of nalbuphine. The decrease in intercept caused by 15 mg was antagonized by naloxone, but antagonism was incomplete. The decrease in intercept caused by 30 and 60 mg was not influenced significantly by administration of naloxone.

The mean log slope of the relationship of $\log_e P_{0.1}$ to PE'_{CO_2} did not change significantly following nalbuphine or naloxone, except following 60 mg in the sitting subjects (table III).

The administration of nalbuphine or naloxone caused no significant changes in mean $P_{0.1}$ at the same VT/TI (table IV).

Plasma nalbuphine concentrations

Mean plasma nalbuphine concentrations after placebo and the three different doses are shown in figure 3. There was a linear relationship between the dose and mean plasma concentration at 30 min ($r = 0.96$). A small quantity of nalbuphine was detected in one sample on the placebo day (JB). This was considered to be a contaminant, as there was no evidence that nalbuphine had been administered inadvertently.

Side effects

Sedation increased significantly following administration of each dose of nalbuphine (fig. 4); no significant difference between the doses could be demonstrated. The effect of naloxone on sedation was not formally tested, but all the subjects were observed to be more alert following naloxone, and after 20 min appeared resedated.

The degree of nausea and vomiting was not related to the dose of nalbuphine. Nausea and vomiting occurred on 10 occasions in 18 subject exposures to nalbuphine, mainly when the subject attempted to sit up. Only one subject (TT) did not complain of nausea or vomiting at some time during the study. In two subjects (JM, JH) nausea and vomiting was severe enought to interrupt the study briefly and the subjects had to remain supine for a few minutes to recover. One subject (JM), who vomited once during the study period, had a small uncomplicated haematemesis 3 h after

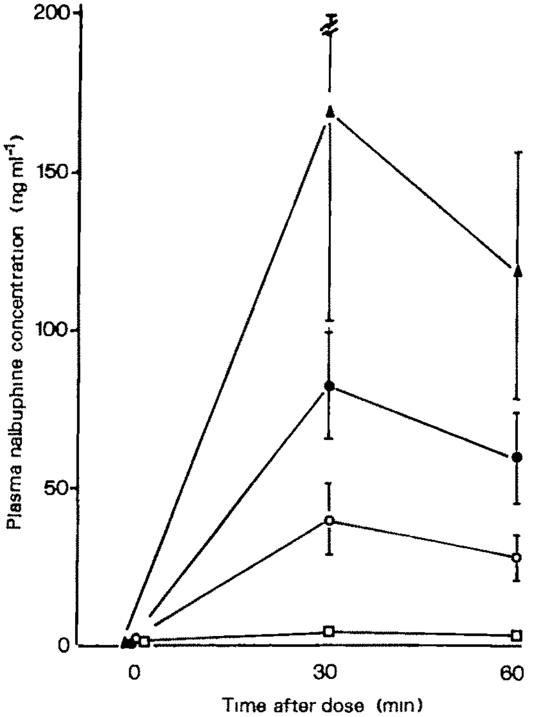

FIG. 3. Mean (SD) plasma nalbuphine concentrations (ng ml^{-1}) at control time and 30 and 60 min after the dose. □ = Placebo; ○ = 15 mg; ● = 30 mg; ▲ = 60 mg.

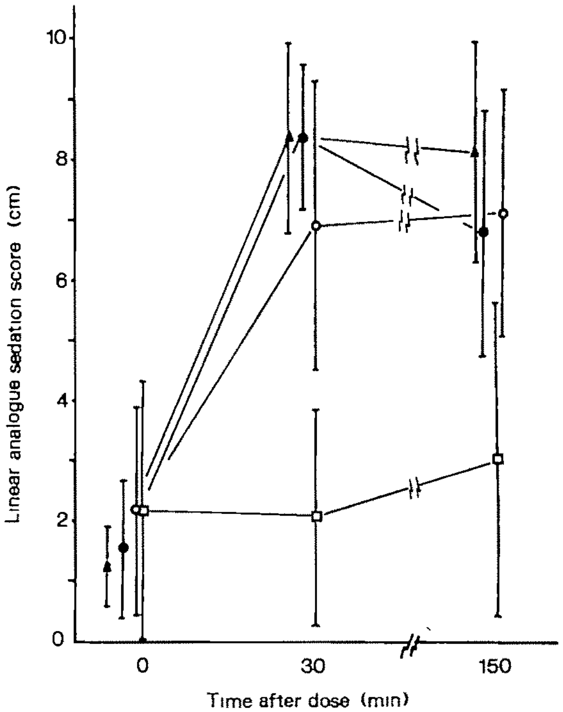

FIG. 4. Mean (SD) sedation linear analogue scores (cm) for the nalbuphine "treatments" at the control time, following nalbuphine and 2 h later. □ = Placebo; ○ = 15 mg; ● = 30 mg; ▲ = 60 mg.

the end of the study. Naloxone did not appear to have an influence on the frequency of nausea or vomiting. Vivid dreams were experienced by 50% of the subjects, and dizziness and pain at the injection site were reported by four subjects. The systolic and diastolic arterial pressures and heart rates remained stable throughout the study.

DISCUSSION

This study was undertaken to determine the effect of nalbuphine on $\dot{V}\text{I}$ and $P_{0.1}$ responses to carbon dioxide, and to analyse possible changes in the relationship between $P_{0.1}$ and $V\text{T}/T\text{I}$. We hoped to determine whether nalbuphine had purely central or central and peripheral effects.

$P_{0.1}$ was measured from when Paw had decreased to -0.1 kPa. This method avoided the difficulty with variation in the onset of the occlusion pressure wave [15] caused by changes in upper airway compliance [16]. Although $V\text{T}/T\text{I}$ increases linearly with $P\text{E}'_{CO_2}$, $P_{0.1}$ does not, and hence the relationship between $V\text{T}/T\text{I}$ and $P_{0.1}$ alters as $P\text{E}'_{CO_2}$ increases, and the "effective impedance" of the system increases with increasing inspiratory flow. Consequently we compared $P_{0.1}$ values that were associated with identical inspiratory flow rates (1 litre s^{-1}), so that the pressure component related to flow would be similar. We used the same inspiratory flow rate, rather than the same $\dot{V}\text{I}$, as $\dot{V}\text{I}$ may be affected by changes in relative duration of inspiration ($T\text{I}/T\text{T}$), despite a constant mean $V\text{T}/T\text{I}$.

Our subjects were unaware of the drug administered, in contrast with previous studies [2, 6, 17]. It was felt less important for the observer to be blinded, as the majority of the assessments were objective. The assessment of sedation was the only subjective measurement, but this was not a major interest of the study.

The results suggest that an Effect maximum (E'max) for ventilatory depression occurred with nalbuphine 15 mg/70 kg or less. With the carbon dioxide rebreathing [2, 17] and the steady-state methods [6, 18] the *E*'max for respiratory depression has been reached with doses of nalbuphine 10.5–30 mg/70 kg. Knoch and colleagues [18] and Romagnoli and Keats [6] administered nalbuphine by different routes. These differences may have accounted for the variations in doses associated with maximal respiratory depression. Although the route and pattern of administration were different, it is of interest that all these investigators [2, 6, 17, 18] and the present study found no further respiratory depression after the lowest dose of nalbuphine had been given. The respiratory depression caused by the three different doses of nalbuphine in this study was equivalent to that observed after morphine 10.5 mg/70 kg [2].

$\dot{V}$I and ventilatory response to carbon dioxide were greater in the sitting than the supine subjects, an observation that is consistent with previous reports [19–21].

Opioid analgesics change the timing of the ventilatory cycle and co-ordination of the muscles of ventilation so that the generation of chest wall movement is altered. Opioids may also change other mechanical factors in the ventilatory system. Thus even if central neural drive were constant, ventilation could change if the effective impedance of the respiratory system were affected. The method proposed by Grunstein, Younes and Milic-Emili [22] has allowed separation of central and mechanical factors. It was proposed that the ventilatory muscles did not shorten during occlusion and that occlusion did not change respiratory neurone discharge [7, 9]. $P_{0\,1}$ has been used as a measure of inspiratory muscle force to assess whether ventilation is reduced by a decrease in available force ($P_{0\,1}$) or by an increase in respiratory impedance ($P_{0\,1}$/ventilation). Using this method, respiratory depression associated with anaesthesia [7], opioid administration [8] and drug overdose [23] has been attributed to an increase in effective impedance. Changes in impedance have also been observed during exercise [24], but not during sleep [25]. However, this approach may be too simple [26]. Direct measurement of muscle fibre length in intact dogs showed that, during airway occlusion, diaphragmatic contraction was not isometric [27]. This observation does not support the premise that neural activation resulted in a muscle force that was not influenced by the force/length and force/velocity relationships of the muscle concerned.

The decrease in $P_{0.1}$ at a given $P\text{E}'_{CO_2}$ in this study suggests that nalbuphine has a direct central respiratory depressant effect. However, for identical inspiratory flow rates, $P_{0\,1}$ remained unchanged before and after administration of nalbuphine. This supports previous findings that nalbuphine has no effect on the impedance characteristics of the lung or chest wall that could influence the translation of inspiratory force into ventilation [2,18].

In this study the changes in $P_{0\,1}$ were not altered significantly by the subject's position. This is a surprising observation, as other assessments of ventilatory mechanics have shown considerable changes with position [19, 28–30]. The pattern of ventilatory muscle activity also changes with position and the relationship between neural activation and mechanical output of the diaphragm is altered [31]. However, a previous study of $P_{0\,1}$ has shown that this index did not alter with posture, despite changes in FRC [32]. These findings and those of others [26] suggest that $P_{0\,1}$ does not permit an exact assessment of the altered respiratory impedance. In particular, changes in the time course of the inspiratory activity within a single breath may conceal alterations in the relationship of muscle activity to lung volume changes [26].

Sedation is a recognized feature of nalbuphine treatment [33, 34] and we confirmed that sedation increased significantly following each dose of nalbuphine. However, we could not determine a significant difference between the doses, suggesting that an *E*'max for sedation may also have been reached.

Changes in respiratory depression with time, following similar single doses of nalbuphine, have been reported by Gal and colleagues [2] and Romagnoli and Keats [6]. They reported maximal respiratory depression between 60 and 120 min and 20 and 40 min, respectively. Because the present study utilized a rebreathing technique similar to that of Gal and colleagues [2], it was decided to administer naloxone 90 min after each dose of nalbuphine. However, no rebreathing study was performed immediately before the administration of naloxone, and the maximal effect of the nalbuphine dose may have passed before naloxone was given. However, after naloxone administration $\dot{V}$I at 7 kPa was still significantly less than control (fig. 1), suggesting that nalbuphine was still active at this time and had not been completely antagonized by naloxone.

Naloxone had no effect on the ventilatory response during the placebo study, confirming earlier findings [35, 36]. Previous studies have reported either complete [2] or incomplete [6] antagonism of the respiratory depressant effects of nalbuphine with naloxone. In the present study naloxone appeared to antagonize the respiratory depression induced by the smallest dose of nalbuphine in the lying subjects. It was clinically significant that the antagonism was incomplete, which supports previous studies [6]. At the higher doses of nalbuphine, and in sitting subjects, no significant antagonism occurred with naloxone even though the ventilatory depression was similar at each dose. This may have been because, in sitting subjects, the depression of ventilation caused by nalbuphine was less marked. A larger dose of naloxone may have been effective.

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PHARMACOKINETICS OF ALFENTANIL DURING AND AFTER A FIXED RATE INFUSION

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SUMMARY

Twenty-nine patients (age range 14–81 yr) undergoing orthopaedic surgery received alfentanil 100 $\mu g\,kg^{-1}$ given as two i.v. boluses followed by a fixed rate infusion of 1 $\mu g\,kg^{-1}\,min^{-1}$ for 44–445 min. Additional 1-mg bolus doses of alfentanil were administered as required. Plasma samples were assayed for alfentanil using radioimmunoassay. Pharmacokinetic parameters were estimated by a model-independent approach and by curve-fitting. Regression analysis showed no statistical relationship between $T_{\frac{1}{2}}^{\beta}$, Cl *or* Vd *and the duration of the infusion, total dose or body weight. We found no significant correlation between age and* $T_{\frac{1}{2}}^{\beta}$ *of alfentanil for patients younger than 40 yr. For patients older than 40 yr,* $T_{\frac{1}{2}}^{\beta}$ *increased linearly with age. There was no significant decrease in* Cl *with age, although the lower values for* Cl *(100–200 ml min^{-1}) were generally found in subjects older than 60 yr. The present study demonstrated that a 100-$\mu g\,kg^{-1}$ loading dose and a 1-$\mu g\,kg^{-1}\,min^{-1}$ infusion may be appropriate for analgesia in general surgical procedures.*

Most information on the pharmacokinetics of alfentanil has been obtained after a single bolus injection in patients under general anaesthesia [1–7]. Maitre [8] used data from four of those studies to calculate a set of average population pharmacokinetic parameters for alfentanil after a bolus injection, using the NONMEM computer program [9, 10]. Sex, body weight and particularly age were noted to be factors affecting the disposition of alfentanil in the normal population of surgical patients without liver or renal function impairment.

There are only a few detailed pharmacokinetic studies of a continuous infusion of alfentanil, despite the clinical importance of this technique [11–13]. Both Fragen and colleagues [11] and Shafter, Sung and White [12] used a two-compartment model in their kinetic analysis, whereas Reitz and co-workers [13] applied a model-independent approach. The pharmacokinetic parameters for alfentanil given by i.v. infusion were similar to those after a single bolus injection, but there were also some conflicting data. Based on a diminished clearance found in two of 11 patients, Reitz [13] claimed that the clearance of alfentanil decreased linearly with duration of infusion. In contrast, Shafer [12] did not find such a correlation. These conflicting findings may be a result of the small numbers of patients included in these studies. Only a few subjects older than 60 yr were included. We have therefore investigated a larger population, using infusions of longer duration.

Using computer predictions based on averaged kinetic parameters, Noorduin and colleagues [14] examined infusion regimens aimed at providing adequate peroperative analgesia whilst avoiding postoperative respiratory depression. Their recommendation for surgery under general anaesthesia was: a fixed rate maintenance infusion of alfentanil 1 $\mu g\,kg^{-1}\,min^{-1}$ preceded by a loading bolus injection of 100 $\mu g\,kg^{-1}$. This should give a therapeutically adequate plasma concentration, at steady state, of 300 ng ml^{-1} [15]. The present study was designed to evaluate these predictions in a patient population with the widest acceptable age range and duration of major peripheral surgery.

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PATIENTS AND METHODS

Twenty-nine patients (19 female) gave verbal consent to participate in the study, which was approved by the local Ethics Committee. All patients were ASA I or II without impairment of hepatic or renal function, and were scheduled for orthopaedic surgery (table I). Mean age was 42 yr (range 14–81 yr), mean weight 70 (50–96) kg, mean duration of infusion 228 (44–445) min. Mean total dose of alfentanil was 24.8 (10.1–45.3) mg.

Patients received either no premedication or diazepam 10 mg by mouth 1 h before surgery. Anaesthesia was induced with an i.v. bolus of alfentanil 50 μg kg^{-1}, vecuronium 100 μg kg^{-1} and thiopentone 2 mg kg^{-1}. After tracheal intubation, the lungs were ventilated mechanically with 70 % nitrous oxide in oxygen to an end-tidal carbon dioxide partial pressure of 3.5–4.5 kPa. An i.v. infusion of alfentanil 1 μg kg^{-1} min^{-1} was started immediately after the initial 50-μg kg^{-1} bolus of alfentanil. A second 50-μg kg^{-1} bolus was administered i.v. immediately before incision, in most cases approximately 30 min after the first bolus. An infusion of vecuronium was started and the infusion rate was adapted to give single twitch depression of 50–75 %. An additional bolus of alfentanil 1 mg was given if an increase in arterial pressure or heart rate of more than 10 % greater than baseline occurred or if the patient responded in other ways to surgical stimulation. The infusions of alfentanil and vecuronium were stopped approximately 20 min before the end of the operation.

TABLE I. *Patient data*

Patient No.	Sex	Age (yr)	Weight (kg)	Duration of infusion (min)	Total dose (mg)
1	F	70	90	241	33.1
2	F	74	68	173	20.3
3	M	32	92	107	18.8
4	M	64	61	230	22.4
5	F	15	80	284	33.5
6	F	18	55	129	13.5
7	M	71	96	178	22.6
8	F	36	56	353	29.1
9	F	58	73	131	17.8
10	F	80	75	220	20.0
11	F	58	61	216	21.5
12	F	81	80	230	27.4
13	M	33	70	44	10.1
14	M	24	92	356	44.8
15	F	48	65	133	15.4
16	F	31	73	150	18.6
17	M	24	78	398	41.4
18	F	31	56	321	29.3
19	F	26	63	237	21.8
20	F	33	75	390	45.3
21	M	15	65	101	12.9
22	M	19	58	347	27.2
23	F	14	50	287	24.3
24	M	26	80	445	45.2
25	M	41	72	173	21.4
26	F	32	70	176	26.0
27	F	42	56	183	16.7
28	F	50	50	192	17.6
29	F	59	72	175	19.9
Mean		42	70	228	24.8
Range		14–81	50–96	44–445	10.1–45.3

Blood samples were obtained from a 20-gauge Teflon cannula inserted into a radial artery, immediately before the first bolus injection of alfentanil and at 5, 10, 20, 30, 45, 60 and every subsequent 30 min during the infusion; further immediately before and 3 and 5 min after each supplementary bolus; and finally 3, 10, 30, 60 and every subsequent 60 min for 8 h after cessation of the infusion.

Analysis

Concentrations of alfentanil in plasma were measured by a specific radioimmunoassay [16]. The detection limit of the assay was 1 ng/ml plasma. The accuracy and reproducibility of the radioimmunoassay were within 5 %. Pharmacokinetic parameters were calculated by two methods: a model-independent approach (MI) and curve fitting (FIT) using standard one-, two- or three-compartment analysis.

In the model-independent approach, the terminal half-life ($T_{\frac{1}{2}}^{\beta}$) and the pharmacokinetic parameters based on the area under the plasma concentration–time curve were calculated. $T_{\frac{1}{2}}^{\beta}$ was obtained as $0.693/\beta$, where β is the slope of the terminal log-linear plasma concentration–time data. The total area under the plasma concentration–time curve ($AUC_{0-\infty}$) was estimated as $AUC_{0-\infty} = AUC_{0-t} + C_t/\beta$ where AUC_{0-t} was obtained using trapezoidal summation to the last plasma concentration (C_t).

All plasma concentration–time curves of alfentanil were fitted to a standard multiexponential equation for a set of i.v. bolus doses and a continuous infusion [17]. Compartmental volume (V_c), α, β and k_{21} were obtained using extended least-squares non-linear regression (ELSFIT) [18]. The appropriate compartmental model was selected by evaluation of the standard errors on the parameter estimates, scatterplots of the residuals between experimental and predicted plasma data and the maximum likelihood function. All other pharmacokinetic parameters were derived using standard methods [17].

The relationships between the relevant pharmacokinetic parameters and variables such as infusion duration, total dose, age and body weight were investigated by linear regression analysis [19].

The estimated steady state concentration (the plasma concentration that would have been reached if the infusion had continued long enough for steady state to be attained) was calculated using the formula: concentration = infusion rate/clearance.

RESULTS

Pharmacokinetic analysis

The pharmacokinetic parameters obtained by the model-independent approach and by curve-fitting are listed in tables II and III, and the two-sided 95% confidence intervals ($t \times$ SEM) for the mean absolute differences between both methods expressed as a percentage of MI are 2–5% for *Cl* and 8–15% for $T_{\frac{1}{2}}^{\beta}$ and Vd^{area} (table IV).

The time course of the alfentanil plasma concentration fitted a two-compartmental model in 26 patients. The plasma concentration data of three patients (Nos 4, 7 and 18) could not be fitted adequately by any compartmental model. We were able to show in the 26 patients whose data could be fitted by both methods that there was no relevant difference between parameters found with our curve-fitting method and those found using a model-independent analysis.

There was a wide variation in $T_{\frac{1}{2}}^{\beta}$ values which ranged from 56 to 226 min. The highest values were found mostly in the age group older than 60 yr.

Effects of dose or duration of the infusion

The duration of the infusions ranged from 44 to 445 min. Total dose ranged from 10.1 to 45.3 mg. There was no significant correlation between the pharmacokinetic parameters ($T_{\frac{1}{2}}^{\beta}$, *Cl*, V_c, Vd^{ss}, Vd^{area}) and the duration of the infusion, or with the total dose including all supplementary i.v. bolus doses.

Effects of body weight

There was no significant relationship between clearance or volume of distribution and body weight.

Effects of age

Vd^{ss} was significantly enlarged with increasing age ($P = 0.003$). Clearance did not correlate significantly with age ($P = 0.16$). Age had a linear effect on $T_{\frac{1}{2}}^{\beta}$ in the patients older than 40 yr ($P = 0.0006$). A correlation was not shown in the patients younger than 40 yr ($P = 0.74$).

Steady state concentration

The mean estimated steady state concentration was 293 (SD 132) ng ml^{-1} (range 147–636 ng ml^{-1}).

TABLE II *Pharmacokinetic parameters derived by model independent approach*

Patient No.	$T_{\frac{1}{2}}^{\beta}$ (min)	*Cl* (ml min^{-1})	Vd^{area} (litre)
1	115	197	32.8
2	155	107	23.9
3	72	401	41.5
4	226	99	32.2
5	80	272	31.3
6	78	194	21.8
7	156	446	100.6
8	94	321	43.7
9	144	171	35.6
10	134	172	33.3
11	78	329	37.2
12	185	198	52.7
13	66	382	36.4
14	70	457	46.3
15	92	332	44.1
16	90	305	39.6
17	79	268	30.4
18	99	181	25.9
19	135	231	45.0
20	94	197	26.8
21	90	218	28.2
22	90	258	33.5
23	77	245	27.2
24	91	178	23.5
25	114	297	48.9
26	96	440	61.1
27	56	362	29.5
28	112	340	54.9
29	102	396	58.5
Mean	106	276	39.5
SD	38	101	15.9

TABLE III. *Pharmacokinetic parameters derived by curve-fitting*

Patient No.	$T_{\frac{1}{2}}^{\alpha}$ (min)	$T_{\frac{1}{2}}^{\beta}$ (min)	k_{10} (min^{-1})	k_{12} (min^{-1})	k_{21} (min^{-1})	V_c (litre)	Vd^{ss} (litre)	Vd^{area} (litre)	*Cl* (ml min^{-1})
1	8.9	132	0.025	0.042	0.016	7.67	27.2	36.4	191
2	6.8	193	0.019	0.068	0.019	5.15	23.3	27.5	99
3	9.9	77	0.038	0.024	0.016	10.13	25.1	43.0	385
4	—	—	—	—	—	—	—	—	—
5	10.3	83	0.024	0.028	0.024	11.78	25.8	33.5	280
6	6.8	80	0.030	0.051	0.029	6.27	17.2	21.9	191
7	—	—	—	—	—	—	—	—	—
8	12.4	94	0.029	0.020	0.014	10.92	26.4	43.4	321
9	2.0	122	0.046	0.265	0.043	4.11	29.6	33.6	191
10	13.9	151	0.015	0.024	0.015	11.25	29.5	37.6	173
11	8.8	96	0.031	0.036	0.018	10.27	30.6	43.7	316
12	15.2	229	0.014	0.025	0.010	13.62	47.3	61.8	187
13	14.1	69	0.026	0.014	0.019	15.96	28.1	42.0	421
14	13.8	72	0.027	0.015	0.018	17.15	31.4	47.5	456
15	12.0	70	0.025	0.020	0.023	13.26	24.6	33.3	332
16	19.8	106	0.020	0.010	0.011	15.11	28.5	47.4	309
17	4.6	77	0.054	0.082	0.025	5.14	21.9	31.2	280
18	—	—	—	—	—	—	—	—	—
19	18.5	140	0.021	0.012	0.009	11.58	28.0	49.9	248
20	21.1	111	0.018	0.010	0.011	11.23	20.7	32.5	203
21	22.8	95	0.014	0.008	0.016	15.55	23.4	30.2	220
22	25.7	97	0.018	0.006	0.011	14.73	22.2	36.5	262
23	22.3	92	0.022	0.006	0.011	11.47	17.9	33.3	251
24	8.7	96	0.027	0.039	0.021	6.53	18.3	24.3	176
25	4.5	83	0.055	0.084	0.023	5.5	25.2	36.2	304
26	7.4	92	0.047	0.039	0.015	9.69	35.0	60.6	456
27	2.4	55	0.076	0.173	0.047	4.85	22.6	29.1	368
28	6.5	131	0.059	0.043	0.010	6.10	33.5	67.6	358
29	12.4	106	0.033	0.018	0.011	11.99	31.8	60.6	395
Mean	12.0	106	0.031	0.045	0.022	10.27	26.7	40.2	284
SD	6.5	39	0.016	0.057	0.018	3.89	6.3	12.0	95

DISCUSSION

Our kinetic parameters correlate well with values obtained in earlier studies after a single dose [1–7] or an infusion [11–13]. The average $T_{\frac{1}{2}}^{\beta}$ was of the order of 2 h and *Cl* was approximately 4 ml kg^{-1} min^{-1} in young to middle-age subjects. In the present study, data of 26 patients were fitted to a two-compartmental model and those from three patients could not be fitted adequately to any compartmental model.

Plasma concentrations after a single bolus injection can usually be fitted to a two-compartmental [3–5] or to a three-compartmental model [1, 2]. However, it is well known that after

TABLE IV. *Comparison of pharmacokinetic approaches. Mean difference and mean absolute difference between the model independent (MI) and the curve fitting (FIT) approaches expressed as a percentage of MI value* (n = 26)

Parameter	Mean difference (95 % confidence limits = 2 × SEM) $100\times\frac{1}{n}\sum_{i=1}^{n}\frac{\text{MI}-\text{FIT}}{\text{MI}}$	Mean absolute difference (95 % confidence limits = 2 × SEM) $100\times\frac{1}{n}\sum_{i=1}^{n}\frac{\lvert\text{MI}-\text{FIT}\rvert}{\text{MI}}$
$T_{\frac{1}{2}}^{\beta}$ (min)	−5.5 (−10.9 to −0.1)	11.3 (7.8–14.8)
Cl (ml min^{-1})	−1.3 (−3.1 to 0.5)	3.3 (2.0–4.6)
Vd^{area} (litre)	−6.4 (−11.4 to −1.4)	10.9 (7.5–14.3)

cessation of an infusion the initial, fast distribution phase is reduced and is discriminated less easily in the total plasma concentration–time profile. This could explain why a three-compartmental model did not improve the fit over a two-compartmental analysis in the present study or in any other infusion study of alfentanil [12, 13]. Shafer, Sung and White [12] found no correlation between clearance and duration of infusion and reported also that the pharmacokinetics were independent of the maintenance infusion rate (0.25–1.3 $\mu g\ kg^{-1}\ min^{-1}$), duration of the infusion (59–385 min), body weight (40–113 kg), age (18–59 yr), sex or type of surgery (superficial or intra-abdominal). In contrast, Reitz and colleagues [13] claimed there is a decrease in clearance and a prolonged half-life with increasing duration of surgery. Visual inspection of their published data reveals no correlation in the nine patients undergoing surgery for less than 150 min and an increase in $T_{\frac{1}{2}}^{\beta}$ and a decrease in *Cl* in only two patients with surgery lasting for 212 and 335 min, respectively. The present study shows that the pharmacokinetics of alfentanil given by i.v. infusion are independent of the duration of the infusion (in our study 44–445 min) and the total dose given (10.1–45.3 mg). Consequently, our data and those of Shafer do not confirm the conclusion drawn by Reitz.

One factor known to change the disposition of alfentanil is age. Helmers [4] found prolonged $T_{\frac{1}{2}}^{\beta}$ and reduced clearance of alfentanil after a single bolus dose in the elderly. In addition, the population pharmacokinetic analysis by Maitre on single-dose data [8], which included the Helmers data from elderly patients, revealed age-related reductions in clearance and a slower redistribution from the deep compartment. With an alfentanil infusion, Shafer's group [12] found no correlation between age and pharmacokinetic parameters, but it has to be stressed that the ages of their patients ranged from 18 to 59 yr. Scott and Stanski [20] reported increased $T_{\frac{1}{2}}^{\beta}$ with age, but they did not find clearance values significantly affected by age. It should be noted that a very short infusion of alfentanil 1500 $\mu g\ min^{-1}$ was given for approximately 5 min, and these data should be considered rather as a slowly given bolus than as a continuous infusion.

Our findings are similar to those of Scott and Stanski [20], with $T_{\frac{1}{2}}^{\beta}$ increased significantly in subjects older than 55 yr, but no significant linear correlation between clearance and age. One reason for the lack of correlation with clearance is probably that this tends to be more variable during a continuous infusion in long-term surgery than after a single bolus injection.

Both the loading dose and maintenance infusion rate in this study were calculated on the basis of body weight, as is conventional practice. The population pharmacokinetic analysis after a single bolus dose by Maitre revealed a significant effect of body weight on the volume of distribution of the central compartment, but not on clearance. In our study, plasma clearance and volumes of distribution (Vd^{ss} and Vd^{area}) did not correlate significantly with body weight.

According to the findings of Ausems and colleagues [15], for adequate pain relief the concentration at steady state should be of the order of 300 $ng\ ml^{-1}$. The mean value of the calculated alfentanil steady-state concentration averaged 293 $ng\ ml^{-1}$ in our study. It indicates that the proposed 100-$\mu g\ kg^{-1}$ loading dose and infusion of 1 $\mu g\ kg^{-1}\ min^{-1}$ may be an appropriate regimen for analgesia in general surgical procedures. As in the present study, transient periods of inadequate analgesia (indicated by hypertension and tachycardia) may be treated by the use of additional i.v. bolus doses of alfentanil 1 mg.

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USE OF MAGNESIUM SULPHATE IN THE ANAESTHETIC MANAGEMENT OF PHAEOCHROMOCYTOMA: A REVIEW OF 17 ANAESTHETICS

M. F. M. JAMES

SUMMARY

Seventeen anaesthetics are described in 16 patients with phaeochromocytoma in whom magnesium sulphate ($MgSO_4$) was the principal anti-adrenergic agent used. In 15 of the 17 anaesthetics, $MgSO_4$ produced satisfactory control of cardiovascular changes at induction and tracheal intubation, but in four of these additional sodium nitroprusside was required to control the arterial pressure during handling of the tumour. In one pregnant patient undergoing Caesarean section, $MgSO_4$ was ineffective in controlling cardiovascular disturbances because of inadequate serum magnesium concentrations. This patient had a magnesium deficit before operation. In another patient, diagnosis was made during operation and $MgSO_4$ provided satisfactory control of the crisis. Catecholamine release was studied in five patients and $MgSO_4$ was found to reduce catecholamine concentrations from the time of induction until tumour handling.

The perioperative management of a patient with phaeochromocytoma is accepted generally to require adequate adrenergic blockade. Preoperative preparation usually entails the use of α-adrenergic blockers such as phenoxybenzamine, with the addition of β-adrenergic blockade, if necessary, to control tachycardia [1]. During operation, control of the effects of excess catecholamine release is usually maintained by deep anaesthesia, coupled with the use of adrenergic blocking drugs such as phentolamine and propranolol, with or without vasodilators such as sodium nitroprusside (SNP). Vasoconstrictors may prove necessary following devascularization of the tumour [1, 2]. Despite all these therapeutic manoeuvres, the total elimination of cardiovascular disturbances is seldom achieved [2].

Magnesium sulphate ($MgSO_4$) has been shown to inhibit the release of catecholamines from both the adrenal medulla [3, 4] and peripheral adrenergic nerve terminals [5], in addition to blocking catecholamine receptors directly. Magnesium also has a direct dilator action on vessel walls [6]. Therefore it appeared worthy of a trial in phaeochromocytoma as an adjunct to conventional therapy. Initial results were encouraging [7] and prompted further study.

PATIENTS AND METHODS

Over a period of 5 years, $MgSO_4$ has been used as an adjunct to the anaesthetic management of 16 patients (age range 14–55 yr; 11 female) on 17 occasions. Details of the patients are shown in table I. Two of the patients were pregnant at the time of presentation. One of these was delivered by Caesarean section and had her tumour resected on a separate occasion (patient No. 4). The other had a malignant phaeochromocytoma for which she had undergone three previous excisions (patient No. 7). Details of these patients have been published elsewhere [8]. Of the remainder, two had tumours that were locally invasive, one involving the right diaphragm and the other invading the left renal vein and inferior vena cava. The first of these patients had pre-existing chronic renal dysfunction (preoperative creatinine clear-

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TABLE I. *Details of patients studied. Phen. = Phenoxybenzamine; praz. = prazosin; prop. = propranolol; aten. = atenolol. RA/LA = Right/left adrenal tumour; diaphragm = diaphragm involved; IVC = inferior vena cava involved; PA = para-aortic tumour*

Patient No.	Age (yr)	Sex	Preparation	Diagnosis	Comments
1	14	F	Phen., prop.	Large RA	Hypertensive in theatre
2	45	F	Phen., prop.	Small RA	Hypertensive in theatre
3	54	M	Phen., prop	Very large RA	Renal disease; diaphragm
4	26	F	Praz., aten.	Small RA	Pregnant; poor control
4	26	F	Praz., aten.	Small RA	—
5	48	M	Phen.	Large LA	Renal vein; IVC
6	22	F	Praz., aten.	Small RA	—
7	24	F	Phen., aten.	Multiple	Malignant; pregnant
8	26	F	Phen., aten.	Small RA	—
9	42	M	Aten., phen.	Small LA	Inadequately prepared
10	34	F	Phen.	Small LA	—
11	32	F	Praz., aten.	Small RA	—
12	51	F	Praz., aten.	Large LA	Hypertensive in theatre
13	39	F	Praz., aten.	Large RA	Hypertensive in theatre
14	28	F	Praz., aten.	Small LA	—
15	55	F	Nil	PA	Diagnosed during op.
16	14	M	Praz., aten.	Large PA	—

ance 42 ml h^{-1}). Two other patients had evidence of target organ damage in the form of a strain pattern on the ECG with inverted T-waves and depressed ST segments in one, and left ventricular hypertrophy in the other. The remaining nine patients had uncomplicated tumours. Tumour size was between 3 cm and 12 cm.

Preoperative preparation

Phenoxybenzamine (eight patients) or prazosin (eight patients) was given in increasing dosage until adequate control of symptoms had been achieved. β-Blockade was added to control tachycardia and fluid replacement given as indicated by cardiovascular measurements. One patient (No. 9) was prepared primarily with β-blockade (atenolol 100 mg twice daily) and phenoxybenzamine 40 mg day^{-1}. Fitness for surgery was judged in accordance with criteria proposed by Roizen [2]. One patient (No. 15) was not prepared before operation as the diagnosis was made at laparotomy.

Premedication was usually with diazepam 10 mg and promethazine 25 mg administered by mouth the night before surgery and again on the morning of operation. Despite this premedication, several of the patients arrived in the operating room with increased arterial pressure. This was regarded as a manifestation of the stress of impending surgery, and not taken as a contraindication to the procedure.

Anaesthetic technique

All patients (except the two who were pregnant) were given fentanyl 3–5 μg kg^{-1} before induction of anaesthesia, followed by $MgSO_4$ 40 mg kg^{-1} i.v. if the systolic arterial pressure (SAP) was within 20 mm Hg of the preoperative value, or 60 mg kg^{-1} if it was greater or the patient was pregnant. Arterial and central venous pressure monitoring cannulae were inserted under local anaesthesia before induction of anaesthesia in all patients.

Anaesthesia was induced with thiopentone and neuromuscular blockade achieved with alcuronium, except in the pregnant patients, in whom suxamethonium was used. If SAP remained increased, a further bolus of $MgSO_4$ 40 mg kg^{-1} was administered before intubation of the trachea. Anaesthesia was maintained with nitrous oxide, oxygen and enflurane (or halothane: patient No. 1). A continuous infusion of $MgSO_4$ 1–2 g h^{-1} was started and maintained throughout the procedure.

SAP was kept within a range of 30 mm Hg greater or less than the preoperative value; increases were managed with up to three further bolus injections of $MgSO_4$ 20 mg kg^{-1} on each occasion, but if this proved insufficient to restore SAP to within the stated limits, SNP was given (table II). Patient No. 15 received $MgSO_4$ only as

TABLE II. *Intra-operative control of cardiovascular events. SNP = Sodium nitroprusside used in addition to* $MgSO_4$*; PH = phentolamine used. SAP1 = Systolic arterial pressure on arrival in the operating theatre; SAP2 = systolic pressure after* $MgSO_4$ *and induction of anaesthesia. See text for definition of stability*

Patient No.	SAP1 (mm Hg)	SAP2 (mm Hg)	Intra-op. SAP range (mm Hg)	Stability	Other agents
1	195	135	120–140	Good	Nil
2	220	115	110–140	Good	Nil
3	215	145	95–180	Fair	SNP
4	220	150	85–220	Poor	SNP, PH
4	130	110	100–140	Good	Nil
5	195	115	110–190	Fair	SNP
6	130	100	100–150	Good	Nil
7	170	150	120–150	Good	Nil
8	186	130	105–150	Good	Nil
9	205	100	100–140	Good	Nil
10	140	95	95–135	Good	Nil
11	150	100	95–140	Good	Nil
12	240	120	100–250	Fair	SNP
13	120	105	100–185	Fair	SNP
14	130	100	90–145	Good	Nil
15	150	175	70–260	Good (after Mg)	Nil
16	130	95	90–200	Good	Nil

intraoperative boluses when the diagnosis had been made. Stability was designated *good* if arterial pressure was maintained within the stated range using $MgSO_4$ alone, *fair* if adequate control could be established by the addition of either SNP or phentolamine, or both, and *poor* if adequate control could not be achieved by any combination. Administration of $MgSO_4$ was discontinued when the tumor had been devascularized. At the end of surgery, neuromuscular blockade was antagonized to an adequate extent as judged by the use of a peripheral nerve stimulator. Serum concentrations of magnesium were measured by atomic absorption spectrophotometry.

Catecholamines

Plasma catecholamine concentrations were measured using a radioimmunoassay technique in five of the last six patients studied. In patient No. 11, catecholamine concentrations were measured before induction, following tracheal intubation, and during periods of tumour handling. In patients 12 and 14, plasma catecholamine concentrations were measured before operation after the initial dose of $MgSO_4$, after the induction of anaesthesia, after tracheal intubation, and during tumour handling. $MgSO_4$ was withheld until after induction of anaesthesia and administered just before intubation in patients 13 and 16, in whom plasma catecholamine concentrations were measured before induction, following induction, after $MgSO_4$, after tracheal intubation and during tumour handling.

RESULTS

$MgSO_4$ provided satisfactory control of SAP and heart rate up to the time of tumour handling in all but one of the patients. In all but one of the patients with increased SAP before induction, arterial pressure was controlled satisfactorily by the use of the combination of magnesium sulphate and fentanyl.

The only failure was in the first of the pregnant patients (patient No. 4, first anaesthetic) in whom no fentanyl was used and therapeutic concentrations of magnesium were not achieved.

One patient had a small (20 mm Hg) increase in SAP with tracheal intubation, and this was the second patient undergoing Caesarean section (patient No. 7) in whom opioids were not administered before intubation.

In 11 of the 17 anaesthetics, $MgSO_4$ alone provided good cardiovascular control throughout the procedure; the case record of the patient controlled least well in this group is shown in figure 1. In four of the remaining six patients, two with locally invasive tumours, and two others with very large tumours, SNP was required also

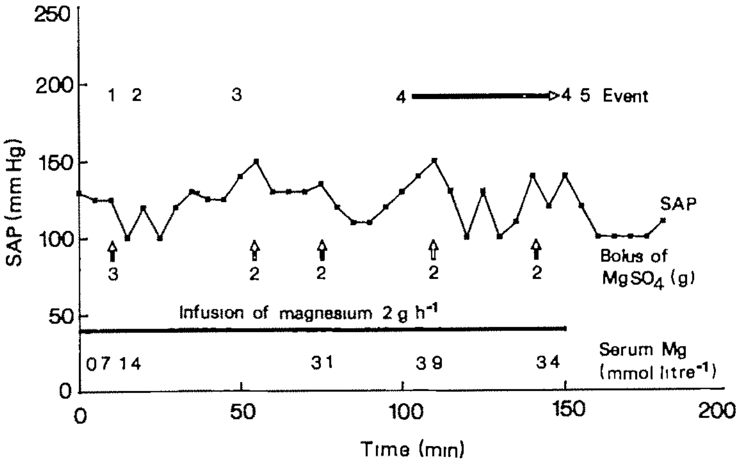

FIG. 1. Systolic arterial pressure changes during anaesthesia in patient No. 6. Event 1 = Induction of anaesthesia; Event 2 = intubation; Event 3 = incision; Event 4 = period of tumour handling; Event 5 = tumour removal.

to control SAP at the time of tumour handling. In two of these patients (Nos 12 and 13), catecholamine concentrations were measured during tumour handling and found to be extremely high, although adequate control was maintained in patient No. 16 despite equally high values.

In the first of the pregnant patients, $MgSO_4$ was without apparent benefit at any stage, but it was subsequently found that therapeutic concentrations of magnesium were not achieved. The greatest serum concentration of magnesium attained in this patient was 1.3 mmol litre^{-1}. In all the other patients, serum magnesium concentrations of between 2 and 4 mmol litre^{-1} were achieved and maintained (this being the presumed therapeutic range based on animal experiments [9], and in obstetric practice [10]).

All patients required supplementary doses of $MgSO_4$ to control increases in SAP at the time of tumour handling. The total dose of $MgSO_4$ administered was in the range 8–18 g with a surgical duration of 60–150 min before tumour devascularization. No arrhythmia occurred in any patient except the one unprepared subject. In this patient (No. 15), the first dose of $MgSO_4$ reduced arterial pressure from its peak of 260/140 mm Hg and controlled arrhythmias. The effect was transient, however, and two further 4-g boluses and one bolus of 2 g were required to obtain a stable state. Serum concentration of magnesium was 3.68 mmol litre^{-1} when cardiovascular control was achieved. In patient No. 16, cardiovascular stability prompted the erroneous assumption that the tumour had been devascularized, but withdrawal of $MgSO_4$ resulted in a rapid increase in SAP, to 200 mm Hg. This responded to further doses of $MgSO_4$.

Two patients in this series required artificial ventilation of the lungs after operation. The first was a 54-yr-old male with a tumour invading the diaphragm, and pre-existing renal dysfunction. In view of his renal disease, the persistence of increased concentrations of serum magnesium was anticipated, but was not considered a contraindication to the procedure as the nature of the surgery made elective postoperative ventilation necessary. Neuromuscular transmission was impaired for 12 h after operation. The indication in the second patient was obesity, although adequate neuromuscular function was restored at the end of the procedure. In all the other patients, neuromuscular blockade was antagonized without difficulty, despite a mean serum magnesium concentration of 1.9 mmol litre^{-1} at the time of antagonism. In the first three patients, calcium gluconate 1 g was administered before antagonism of neuromuscular blockade, but this appeared unnecessary and was omitted in the later patients.

Greatly increased plasma concentrations of adrenaline and noradrenaline were found in the five patients in whom they were measured on arrival in the operating theatre. Noradrenaline concentrations were in the range 1900–9432 pg ml^{-1} (normal range 100–600 pg ml^{-1}) and adrenaline concentrations were 120–390 pg ml^{-1} (normal range 10–80 pg ml^{-1}). Dopamine values were

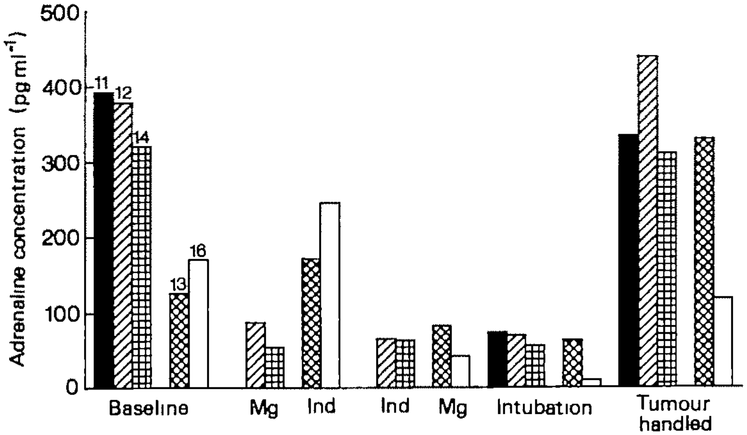

FIG. 2. Changes in adrenaline concentrations in patients 11, 12, 14, 13 and 16 (identified by numbers over first set of columns) during anaesthesia for excision of phaeochromocytoma. Mg = administration of $MgSO_4$; Ind. = induction of anaesthesia.

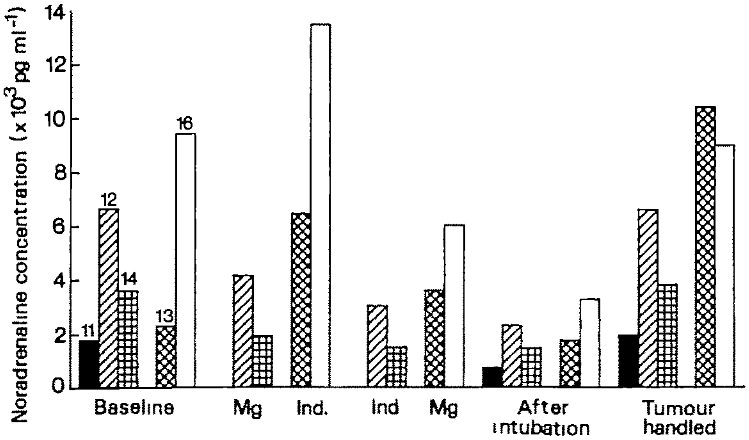

FIG. 3. Changes in noradrenaline concentrations in patients 11, 12, 14, 13 and 16 (identified by numbers over first set of columns) during anaesthesia for excision of phaeochromocytoma Ind. = induction of anaesthesia; Mg = administration of $MgSO_4$.

normal. $MgSO_4$ reduced noradrenaline and adrenaline concentrations in all patients, adrenaline concentrations to within the normal range, but noradrenaline concentrations to values which, although reduced, remained greater than normal. In the two patients in whom anaesthesia was induced before administration of $MgSO_4$, concentrations of noradrenaline and adrenaline increased following induction, and returned to or below pre-induction values following administration of $MgSO_4$. No increase in catecholamine concentrations occurred following intubation. During handling of the tumour, $MgSO_4$ was ineffective in blocking the release of catecholamines. Noradrenaline concentrations were very high in two patients, and SNP was required to control SAP during tumour handling. In the other three patients, $MgSO_4$ alone provided adequate control. The changes in catecholamine concentrations are illustrated in figures 2 and 3.

One patient developed severe hypotension following tumour removal in association with massive blood loss. Blood transfusion and vasoconstrictors failed to restore SAP and an infusion of adrenaline was required for the remainder of the surgery and 24 h afterwards. This patient (No. 9) had been prepared for surgery principally with β-blockade, the effects of which may have persisted after tumour excision. As he continued to require adrenaline for a long period after serum concentrations of magnesium had returned to normal, it seems unlikely that the hypotension was caused by $MgSO_4$, although this possibility cannot be entirely discounted.

The only other complication was an unpleasant burning sensation produced by the $MgSO_4$ infusion. This only occurred in the second of the Caesarean section patients, in whom $MgSO_4$ was given without the prior administration of any analgesic or sedative drugs. Although this problem is well known to occur with the i.v. infusion of $MgSO_4$, the concomitant use of fentanyl appeared to prevent this complication in the other patients.

DISCUSSION

The rationale for the use of $MgSO_4$ infusions in the anaesthetic management of phaeochromocytoma is based on the ability of magnesium to inhibit the release of catecholamines from the adrenal medulla [3–5, 11], to reduce the sensitivity of α-adrenergic receptors to catecholamines [12], and to exert a direct vasodilator effect [6]. The serum concentration of magnesium required to exert these effects appears to be in the range 2–4 mmol $litre^{-1}$ [9–12]. The ability of $MgSO_4$ infusions to control catecholamine-induced crises and reduce catecholamine concentrations associated with severe tetanus has been described [13–15]. The safety of $MgSO_4$ in the serum concentrations achieved in this series is well established [10, 16].

In the five patients in whom catecholamine concentrations were studied, $MgSO_4$ reduced adrenaline concentrations to within the normal range and also reduced noradrenaline concentrations, although not to values approaching normal. The greater effect on adrenaline may result from its shorter half-life with, therefore, a more rapid clearance following the inhibition of release from the tumour. Although the stress of tracheal intubation is known to release catecholamines [17, 18], no increase was demonstrated in the patients studied. The role of $MgSO_4$ in inhibiting the release of catecholamines during tumour handling is uncertain. Magnesium blocks catecholamine release by competition with calcium for membrane channels [3–5], and it seems unlikely that this action would be important during physical stimulation of the tumour.

In addition to its action in blocking catecholamine release, magnesium has inherent cardiovascular activity [19], which could be of benefit during anaesthesia in patients with phaeochromocytoma. Its direct vasodilating properties are well established *in vitro* and *in vivo* [19–26]. Magnesium reduces the sensitivity of blood vessels *in vitro* to the action of various vasoconstrictors, including noradrenaline [26–28], and antagonizes the adverse effects of high concentrations of circulating adrenaline in intact animals [29].

The results of this present study are in apparent conflict with those in pre-eclampsia, where $MgSO_4$ appears to produce only mild hypotension, although profound hypotension has been described in association with a blood volume deficit [30]. There are several possible explanations for this. First, the dose regimens for $MgSO_4$ generally used in obstetric practice frequently fail to produce the desired serum concentrations of magnesium [31]. In the present study, very large doses of $MgSO_4$ were needed to maintain the serum magnesium concentration within the required range. Second, the increase in cardiac output demonstrated in both animals and man [9, 32, 33] largely offsets the hypotensive effect of the vasodilation induced by magnesium. Third, the reduction in peripheral resistance produced by magnesium appears to be greater in the presence of high concentrations of catecholamines than when they are normal [29], probably because of the α-blocking properties of the ion. Further, the reduction of catecholamine concentrations in patients with phaeochromocytoma not only enhances the vasodilator effect, but also reduces cardiac output [14]. It is not surprising, therefore, that the cardiovascular effects of $MgSO_4$ infusions should be greater in patients with phaeochromocytoma than in obstetric patients.

Magnesium is a potent anti-arrhythmic agent [34–36], particularly in the presence of high concentrations of catecholamines [29], and no patient in this series developed intraoperative arrhythmias, even when there was massive release of catecholamine. This was in contrast to the frequency of transient intraoperative arrhythmias seen with most other agents [2]. In the unprepared patient, arrhythmias were controlled completely by $MgSO_4$. Magnesium has been shown also to limit the production of lactate by the myocardium during catecholamine stimulation, without interfering with the inotropic action of adrenergic agents [37]. Use of this agent may offer, therefore, biochemical protection to the myocardium in the presence of high catecholamine concentrations.

The rarity of phaeochromocytoma makes controlled trials difficult. As this series of patients was collected over several years and the patients were not prepared consistently, a controlled trial of magnesium was not feasible. Nevertheless, the ease of management of these patients, particularly during the induction and early surgical phases of the procedure, was in marked contrast to the author's personal experience of 10 patients managed previously by conventional means. Whilst other anti-adrenergic and vasodilator agents are more potent than $MgSO_4$, the unique capacity of magnesium to inhibit the release of catecholamines before tumour handling is probably the principal reason for the cardiovascular control obtained in this series.

$MgSO_4$ thus appears to be a useful addition to the armamentarium available for the anaesthetic management of patients with phaeochromocytoma. It seems to be of particular value in controlling cardiovascular disturbances and catecholamine release at the times of induction and intubation, but may also be of use, in conjunction with other agents, in controlling arrhythmias and arterial pressure disturbances during periods of tumour handling.

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RETROSPECTIVE STUDY OF EARLY POSTOPERATIVE CONVULSIONS AFTER INTRACRANIAL SURGERY WITH ISOFLURANE OR ENFLURANE ANAESTHESIA

A. R. CHRISTYS, E. MOSS AND D. POWELL

SUMMARY

Retrospective analysis of the case records of 383 patients undergoing elective intracranial surgery showed that, in the first 24 h after surgery, 13.9% of patients receiving low concentrations (0.4–1 MAC) of isoflurane had one or more convulsions after operation, compared with 8% receiving enflurane (0.4–1 MAC). Controlled ventilation was required as part of the therapy for convulsions in 4.9% of the isoflurane group and 3.6% of the enflurane group. These differences between the groups were not statistically significant.

Convulsions increase cerebral activity and may cause cerebral hypoxia if oxygen demand exceeds supply. This may be disastrous for a brain compromised by surgery.

Following the introduction of isoflurane into neuroanaesthesia, in our practice there appeared to be an increase in the number of patients having early postoperative fits, many requiring admission to the intensive care unit for treatment of repeated convulsions. At the same time, case reports were published describing seizures during isoflurane anaesthesia [1,2]. We have therefore compared the frequency of convulsions after isoflurane and enflurane anaesthesia for elective intracranial surgery.

PATIENTS AND METHODS

We studied 391 consecutive patients who had undergone elective intracranial surgery for a wide range of supratentorial and infratentorial lesions, from January 1985 to August 1987. The medical and nursing records, anaesthetic charts and discharge summaries were reviewed to find the number of patients who had one or more convulsions in the first 24 h after surgery. The intensive care records revealed which patients required controlled ventilation.

Throughout the study, patients who had supratentorial intracranial tumours or who were undergoing clipping of middle or anterior cerebral artery aneurysms were given anticonvulsant prophylaxis with either phenytoin 300 mg daily or sodium valproate 1 g twice daily for at least 24 h before surgery. Routine anticonvulsant medication was continued throughout the perioperative period in patients who had convulsions before operation.

The anaesthetic procedure was the same in all patients, with the exception that the volatile anaesthetic agent used varied. Unless the patient was drowsy, diazepam 10 mg or temazepam 20 mg was given before operation. Anaesthesia was induced with thiopentone and fentanyl, and tubocurarine or atracurium was used to facilitate tracheal intubation. The lungs were ventilated to maintain mild hypocapnia (Pa_{CO_2} 3.5–4.0 kPa) with 66% nitrous oxide and either isoflurane or enflurane in inspired concentrations of 0.4–1 MAC in oxygen. The concentration of volatile anaesthetic agent was adjusted according to the patient's requirements. Further doses of fentanyl and tubocurarine or atracurium were given as required. For some procedures, hypotension was induced with trimetaphan or a mixture of trimetaphan and sodium nitroprusside.

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TABLE I. *Intracranial operative procedures*

	Isoflurane	Enflurane
Clipping of aneurysm	69 (28%)	33 (24%)
Anterior communicating aneurysm	16 (6.5%)	9 (6.5%)
Arteriovenous malformation	5 (2%)	2 (1.5%)
Supratentorial tumour	98 (40%)	56 (40.5%)
Infratentorial tumour	28 (11%)	23 (17%)
Haematoma	2 (1%)	3 (2%)
Temporal lobectomy	2 (1%)	2 (1.5%)
Microvascular decompression of the 5th nerve	17 (7%)	7 (5%)
Pituitary tumour	13 (5%)	7 (5%)
Posterior fossa decompression	1 (0.5%)	2 (1.5%)
Supratentorial cerebral abscess	5 (2%)	1 (0.5%)
Dural repair	5 (2%)	2 (1.5%)
Total	245	138
Supratentorial	197 (80.4%)	105 (76.1%)
Infratentorial	48 (19.6%)	33 (23.9%)

The electrocardiogram, direct arterial pressure and end-tidal carbon dioxide concentration were monitored.

Data were analysed using the Chi-square test. The Yates' correction factor was used as appropriate.

RESULTS

Complete records were obtained in 383 of the 391 consecutive patients. In eight patients (six isoflurane and two enflurane), records were incomplete, and these were excluded from the study.

The distribution of the operative procedures was similar in the two groups (table I). Convulsions occurred before operation in 16.8% of the patients in the isoflurane group and 18.4% in the enflurane group. The incidence of convulsions in the first 24 h after surgery was 13.9% in the isoflurane group and 8% in the enflurane group; this difference was not significant (table II). Of the patients who had postoperative convulsions, 19.5% in the isoflurane group and 16% of those given enflurane had convulsed before operation. As part of their treatment, 4.9% of the patients in the isoflurane group and 3.6% in the enflurane group (ns) required admission to the intensive care unit for intermittent positive pressure ventilation.

More detailed analysis of the records of those patients who had postoperative convulsions did not show any consistent pattern with regard to the presence of convulsions before operation, type of premedication, use of preoperative anticonvulsants or neuromuscular blockers, neurosurgeon, anaesthetist or the use of induced hypotension. However, patients having supratentorial intracranial operations were more likely to have convulsions after operation than those having posterior fossa surgery ($0.01 > P > 0.001$). Of the supratentorial operations, only clipping of anterior communicating artery aneurysms was associated with a significantly increased likelihood of postoperative convulsions ($P < 0.001$).

DISCUSSION

The frequency of early postoperative convulsions after craniotomy ranges from 2% to 72% [3,4]. Jennett has suggested that they may be of prognostic significance for the persistence of epilepsy as occurs after head injury [5]. There has been no previous study comparing the effects of isoflurane and enflurane on the incidence of convulsions following intracranial surgery. In this study, the overall frequency of convulsions in the early postoperative period was 11.7%, with a similar frequency following isoflurane and enflurane. In 4.4% of the patients, controlled ventilation was required to control repeated convulsions. Although it has been reported that the incidence of convulsions after intracranial surgery is increased in patients who have had fits before operation [6], this association was not observed in our patients.

This study was retrospective, so it is possible that some unknown factor has introduced bias. However, the two study groups were comparable

TABLE II. *Incidence of convulsions before operation and in the first 24 h after surgery*

	Isoflurane	Enflurane
Preoperative convulsions (%)	16.8	18.4
Convulsions in the first 24 h after surgery (%)	13.9	8
Required IPPV for control of convulsions	4.9	3.6

with respect to frequency of preoperative convulsions and proportion of supratentorial and posterior fossa operations. In addition, historical bias may be excluded because the same consultant surgeons were operating, or supervising the operations, throughout the period of the study and no new operative procedures were introduced during this time.

Isoflurane and enflurane in concentrations of up to 1.5 MAC have similar effects on the electroencephalogram (EEG) [7]. Initially, they cause low voltage–high frequency activity, but as the inspired concentration increases to approximately 1 MAC, high voltage (110–150 µV) slow waves occur [7–9]. Higher concentrations of isoflurane depress the EEG, with burst suppression and a decrease in frequency and voltage until the EEG becomes isoelectric [8]. In contrast, higher concentrations of enflurane cause spike and wave complexes on the EEG, particularly in association with hypocapnia and auditory stimulation [10].

EEG abnormalities and seizures have been reported during and after enflurane anaesthesia [10–12]. There are also case reports of seizures during or after anaesthesia with isoflurane [1,2, 13], but these have been criticized on the grounds that in one case nitrous oxide and fentanyl [14] and in another nitrous oxide [15] may have been responsible. Animal work suggests that seizure activity may be potentiated by nitrous oxide [16], thiopentone, methohexitone and diazepam [17]. Unusual EEG changes and one postoperative convulsion were described when isoflurane was used during cardiopulmonary bypass in children [18]. Conversely, isoflurane has been used in the treatment of status epilepticus [19].

Isoflurane has advantages in neuroanaesthetic practice [20]. It causes less increase in cerebral blood flow than enflurane or halothane [21], it preserves the responsiveness of the cerebral circulation to changes in arterial carbon dioxide concentration [22] and, in concentrations of up to 1.0 MAC, cerebral autoregulation is maintained [23]. Isoflurane has little effect on intracranial pressure [24,25] or cerebrospinal fluid production or reabsorption [26,27], and cerebral protective properties have been claimed [28,29], but are disputed [30,31]. It can be used safely to produce moderate hypotension [32,33] and does not mask the EEG signs of cerebral ischaemia during carotid endarterectomy [34]. However, a potential to precipitate postoperative convulsions would reduce its usefulness in anaesthesia for intracranial surgery.

It is well known that supratentorial intracranial operations are associated with postoperative convulsions and that aneurysm surgery is a predisposing factor [6]. It has been reported also that almost 80% of first postoperative fits occur within the first 24 h after surgery [3]. These data support the conclusion that the neurosurgical procedures precipitated the fits in our patients and that the anaesthetic agents were not to blame. In this study, 48% of patients undergoing clipping of an anterior communicating artery aneurysm had a convulsion in the first 24 h after surgery, and it seems that this operation is particularly likely to precipitate convulsions.

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COMPARISON OF THE EFFECTS OF HIGH FREQUENCY OSCILLATION AND CONTROLLED MECHANICAL VENTILATION ON HYALINE MEMBRANE FORMATION IN A RABBIT MODEL OF THE NEONATAL RESPIRATORY DISTRESS SYNDROME

D. J. NIBLETT, B. K. SANDHAR, M. S. DUNNILL AND M. K. SYKES

SUMMARY

Saline lavage of the lungs of eight anaesthetized New Zealand White rabbits was performed to produce a surfactant-depletion model of the neonatal respiratory distress syndrome. A characteristic change in the shape of the pressure–volume curve occurred, with the appearance of an inflection point on the inspiratory limb. The animals were treated with high frequency oscillation (HFO) at 15 Hz and the results compared with those of a previously studied group of eight similar rabbits treated with controlled mechanical ventilation (CMV) with end-expiratory pressure equal to the pressure at the inflection point, but with the same mean airway pressure of 15 mm Hg. The animals treated with HFO had significantly higher arterial oxygen tensions and end-expiratory lung volumes than those treated with CMV, but there was no significant difference between hyaline membrane scores. Although there was no significant difference in mean survival times, five of the HFO treated animals showed reversion of the shape of their pressure–volume curves towards the pre-lavage configuration, suggesting a recovery of surfactant function.

The characteristic features of the neonatal respiratory distress syndrome (NRDS) are surfactant deficiency and alveolar capillary damage. These changes lead to leakage of fluid into the pulmonary interstitium and alveoli and regional reductions in lung compliance, which result in non-uniformity of lung expansion and intra-regional stresses when the lungs are ventilated. It has been postulated that such stresses occurring during controlled mechanical ventilation (CMV) may play an important role in the aetiology of pulmonary damage and may result in hyaline membrane formation [1].

Several ventilatory techniques have been used to minimize these stresses, including: high frequency oscillation (HFO), with a respiratory frequency of 15 Hz [1]; CMV with high positive end-expiratory pressure [2]; apnoeic oxygenation with extracorporeal carbon dioxide removal ($ECCO_2R$) [3, 4]; instillation of artificial surfactant [5].

As other workers have failed to demonstrate beneficial effects from the use of either HFO [6], or high frequency jet ventilation [7], we have studied the effects on oxygenation and the severity of hyaline membrane formation of HFO at 15 Hz, and compared the data obtained with those from CMV with high PEEP, in surfactant depleted rabbits.

MATERIALS AND METHODS

We studied eight New Zealand White rabbits (weights 1.5–2.5 kg). With the animal in a box, anaesthesia was induced using 4% halothane in 100% oxygen and Hypnorm 0.2 ml kg^{-1} (Janssen: fentanyl 0.3 mg + fluanisone 10 mg in 1 ml) given i.m. after 15 min. A 22-gauge venous cannula

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was inserted in the left ear and 9-mg doses of pentobarbitone were given whilst tracheotomy was performed. A 4-mm i.d. plastic tracheal tube was inserted via the tracheostomy and secured in place with ligatures to prevent leaks. Pancuronium 1 mg was given i.v. to produce apnoea and anaesthesia was maintained with an i.v. infusion delivering Hypnorm 50 μl and pancuronium 1 mg in 0.9% saline at a rate of 5 ml h^{-1}.

The lungs were ventilated initially with a fresh gas flow of 350 ml kg^{-1} and an I:E ratio of 1:1 at 25 b.p.m., whilst carotid arterial and right ventricular cannulae were inserted for pressure monitoring and blood sampling. The right ventricular cannula used was a 5-French gauge pulmonary artery catheter, inserted via the internal jugular vein. $FI_{O_2} = 1$ was maintained throughout the study. The ECG and rectal temperature were monitored in all animals. After samples of arterial and mixed venous blood had been obtained, a pressure–volume (P–V) curve was recorded by injecting aliquots of air into the lungs at 3-s intervals to a total of 20 ml. The sequence of inflation volumes used was 3, 5, 10, 15 and 20 ml in all animals. Lung damage was produced subsequently by lavage with 20-ml kg^{-1} aliquots of 0.9% saline, at 37 °C, in a manner similar to that described previously [8]. The saline was syringed directly into the tracheal tube whilst the airway pressure was monitored to ensure that it did not exceed 25 mm Hg. The saline was aspirated and ventilation reinstituted immediately with a PEEP of 2–3 mm Hg. Five minutes later, arterial blood-gas tensions were measured and the lavage repeated until the arterial PO_2 was less than 10 kPa. This was usually achieved by three to six lavages. Ventilation was continued for a further 15 min following the final lavage, when a P–V curve was determined and the inflection point identified.

The animals then underwent ventilation by HFO at a frequency of 15 Hz. The mean airway pressure was maintained at 14–16 mm Hg by the application of PEEP to the expiratory limb of the circuit. The tidal volume was adjusted according to the Pa_{CO_2}. Sodium bicarbonate 4.2% was given as necessary to correct the base deficit which developed. The animals underwent ventilation inside a whole body plethysmograph to permit hourly measurements of the end-expiratory lung volume (EELV) (the volume in the lungs in excess of functional residual capacity) by opening the breathing circuit to atmosphere and recording the change in pressure within the box. At 1-h intervals, the following sequence of readings was made: arterial blood-gas tensions and arterio-venous oxygen content difference ($Ca_{O_2} - C\bar{v}_{O_2}$); EELV; P–V curve. Ventilation was reinstituted at peak inflation of the lungs.

Ventilation was continued in this manner, until 5 h had elapsed, when the animal was killed, or until death if this occurred earlier. The lungs were immediately excised and inflated to 20 cm H_2O with formol–saline before fixation in this solution. Multiple sections taken from different parts of the specimens were stained with haemotoxylin and eosin for histological examination as described previously [2]. The severity of hyaline membrane formation and intra-alveolar neutrophil infiltration were scored on a scale of 0–4 by one of the authors (M.S.D.), who was unaware of the group from which the specimen was drawn. The scores of the right lungs were compared, as some of the left lungs of the animals treated with HFO were used for measurement of wet:dry ratios for later use.

Instrumentation

High frequency oscillations were produced by a fixed-stroke diaphragm pump driven by a variable speed electric motor (fig. 1). A silastic tube of length 1 m and internal diameter 7.5 mm delivered the oscillations to the tracheal tube via a T-piece. A variable leak from this tube allowed the stroke volume (and thus tidal volume) to be altered. A bias flow of oxygen 10 litre min^{-1} was delivered to the tracheal tube via narrow bore oxygen tubing. The expiratory limb consisted of reinforced tubing (i.d. 12.5 mm × 5.7 m long) which acted as a low pass filter. PEEP was provided by a magnetic valve (Instrumentation Industries), situated downstream from a 2-litre glass bottle which acted as a reservoir to reduce valve flutter.

Arterial, right ventricular and airway pressures were measured by Druck transducers connected to a Lectromed M19 chart recorder. A Validyne MP45 transducer was used to monitor volume changes in the plethysmograph. Blood-gas tensions were measured by an ABL2 automated analyser (Radiometer, Copenhagen). Arterial and mixed venous oxygen contents were measured using a Lex-O_2-Con analyser (Lexington Instruments).

The results were compared with those from a

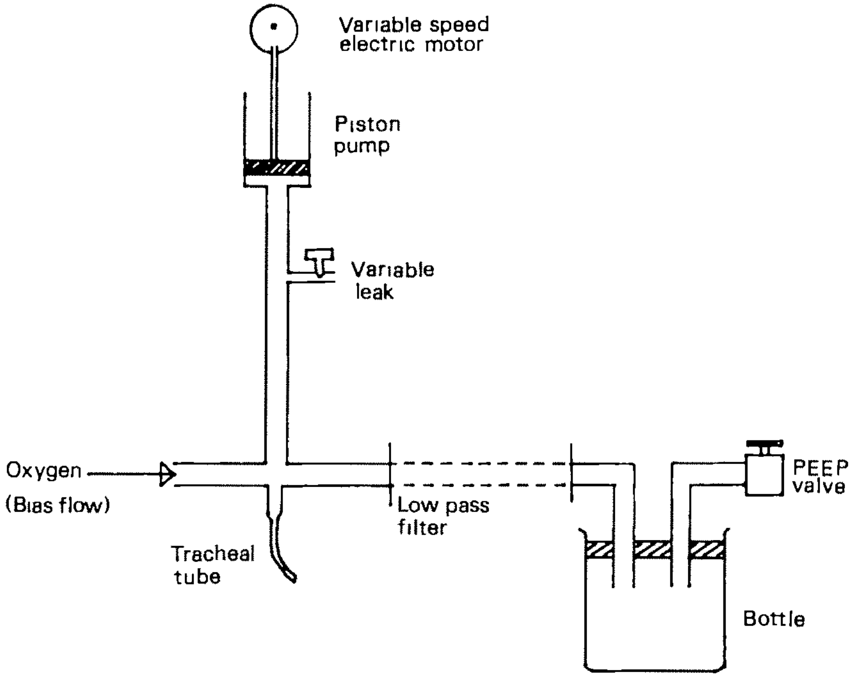

FIG. 1. Diagrammatic representation of the system used to deliver high frequency oscillations to the rabbits.

group of eight rabbits treated previously in the same way, but with their lungs ventilated by CMV with PEEP set at the level of the measured inflection point pressure [2].

Statistical analysis of the results was performed using the Mann–Whitney *U* test or Wilcoxon rank sum test for non-parametric data to compare the hyaline membrane and neutrophil infiltration scores and the data from the two groups at each stage of the experiment, and to examine the effects of lavage in each group. A one-way analysis of variance was used to examine changes with time within each group.

RESULTS

There were no significant differences between the mean weights of the two groups of animals, or between their pre-lavage blood-gas tensions, ($Ca_{O_2} - C\bar{v}_{O_2}$) or airway pressure measurements. The P–V curves (for inflation to 20 ml) showed mean lung compliances of 4.9 (SD 1.0) ml/mm Hg in the CMV group and 5.8 (2.1) ml/mm Hg in the HFO group, with no significant differences.

As reported in previous studies [2, 9] the P–V curves showed characteristic changes after saline lung lavage, with the appearance of an inflection point on the inspiratory limb. The mean pressure at the inflection point (P_{infl}) was 10.5 (1.9) mm Hg in the CMV group and 9.7 (1.6) mm Hg in the HFO group. At pressures below this point, lung compliance was low. Above the inflection point, the slope was similar to pre-lavage values in the CMV group, but reduced in the HFO group (pre-lavage 5.8 (2.1); post-lavage 3.9 (1.1) ml/mm Hg; $P = 0.03$). There was a significant decrease in Pa_{O_2} as a consequence of lavage ($P < 0.001$ in both groups) and a significant increase in Pa_{CO_2} of a comparable degree in both groups ($P < 0.005$), but no changes in base excess were observed. A similar number of lavages was needed in the two groups of animals to achieve the same reduction in Pa_{O_2} (mean 8.1 (1.1) in the CMV group; 9.1 (1.9) in the HFO group).

Stabilization of the animals following lavage on both CMV with PEEP and HFO led to a marked improvement in arterial oxygenation. The Pa_{O_2} values were, however, consistently greater in the HFO animals throughout the course of the experiment (table I, fig. 2) ($P < 0.008$).

TABLE I. *Mean (SD) of arterial oxygen (Pa_{O_2}) and carbon dioxide (Pa_{CO_2}) tension, base excess (BE) and the arterio–venous oxygen content differences ($Ca_{O_2}-C\bar{v}_{O_2}$) at each stage of the experiment in the two groups of animals. Significant difference from PEEP*: *$P \leqslant 0.05$; **$P \leqslant 0.001$

Time	Group	Pa_{O_2} (kPa)	Pa_{CO_2} (kPa)	BE (mmol litre^{-1})	($Ca_{O_2}-C\bar{v}_{O_2}$) (vol %)
Pre-lavage	PEEP	62.7 (7.6)	4.1 (0.7)	−0.4 (3.5)	6.3 (1.6) ($n = 6$)
	HFO	65.6 (6.3)	4.6 (0.5)	−3.1 (3.4)	8.0 (1.6)
Post-lavage	PEEP	8.1 (1.1) ($n = 7$)	5.3 (0.7) ($n = 7$)	−2.0 (2.9) ($n = 6$)	—
	HFO	9.1 (1.9)	6.0 (0.9)	−5.5 (3.0)*	6.2 (1.0) ($n = 6$)
1 h	PEEP	37.9 (18.9)	4.6 (1.1)	−4.0 (5.5)	6.3 (2.2) ($n = 6$)
	HFO	63.9 (11.7)*	3.3 (0.7)*	−5.6 (3.6)	7.8 (2.0)
2 h	PEEP	39.6 (21.8)	5.1 (1.0)	−4.8 (2.1)	7.9 (2.7) ($n = 6$)
	HFO	67.7 (14.5)**	3.4 (0.7)*	−8.0 (5.6)	8.6 (1.8)
3 h	PEEP	41.1 (20.2)	5.0 (1.0)	−7.1 (3.6)	8.4 (2.2) ($n = 6$)
	HFO	71.8 (7.6)**	3.4 (0.9)*	−7.7 (5.9)	8.0 (2.1)
4 h	PEEP	33.6 (21.8) ($n = 6$)	5.5 (0.7) ($n = 6$)	−5.0 (4.8) ($n = 6$)	7.5 (2.1) ($n = 4$)
	HFO	66.4 (7.0)* ($n = 6$)	3.3 (0.8)** ($n = 6$)	−7.9 (5.7) ($n = 6$)	9.0 (2.3) ($n = 6$)
5 h	PEEP	29.3 (18.4) ($n = 6$)	5.0 (1.2) ($n = 6$)	−8.1 (3.6) ($n = 6$)	7.3 (0.8) ($n = 2$)
	HFO	52.3 (23.3) ($n = 5$)	3.3 (0.8)* ($n = 5$)	−9.0 (7.8) ($n = 5$)	9.2 (2.1) ($n = 5$)

Although attempts were made to maintain Pa_{CO_2} within normal limits by adjustment of the fresh gas flow and ventilatory rate, we were unable to prevent hypocapnia in the animals treated with HFO (table I). All the animals developed a progressive increase in base deficit, despite attempts to correct the pH by infusion of bicarbonate (table I). There was no significant difference between the base deficit in the two groups.

The peak airway pressures remained higher in the CMV group throughout the study ($P = 0.001$) (table II), the greatest mean peak airway pressure in the CMV group being 26.9 (3.4) mm Hg at 3 h, with a mean value in the HFO group of 15.8 (1.4) mm Hg at this time. Mean airway pressures were maintained the same (15 mm Hg) in both groups. The mean ($Ca_{O_2}-C\bar{v}_{O_2}$) values were similar in both groups throughout the 5-h study period (table I).

The mean EELV were significantly higher in the HFO animals at all stages except the 5th hour (table III). The lowest EELV in the HFO group was 39 ml, but the EELV values in the CMV group were much more variable, two of the animals showing EELV equivalent to those of the HFO group throughout.

There was no significant difference between either the hyaline membrane or neutrophil infiltration scores of the two groups of animals (table IV) ($P < 0.05$). The mean survival times were similar (CMV 262 (58) min; HFO 270 (45) min).

During the 5-h experimental period, the P–V curves in five of the eight HFO animals showed a change from their immediate post-lavage shape, tending to lose their marked inflections (fig. 3). This is reflected in the improvement in the lung compliance below P_{infl} in the HFO animals (table III) which was significantly greater than that of the CMV animals ($0.02 < P > 0.005$), except at 5 h. Two of the eight animals treated with CMV also showed some overall improvement in lung compliance.

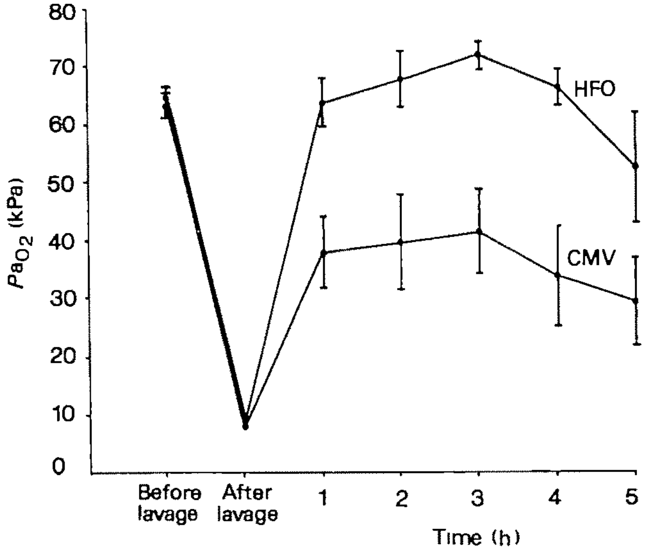

FIG. 2. Mean arterial oxygen tensions during the course of the experiment in the two groups of animals. HFO = High frequency oscillation; CMV = controlled mechanical ventilation.

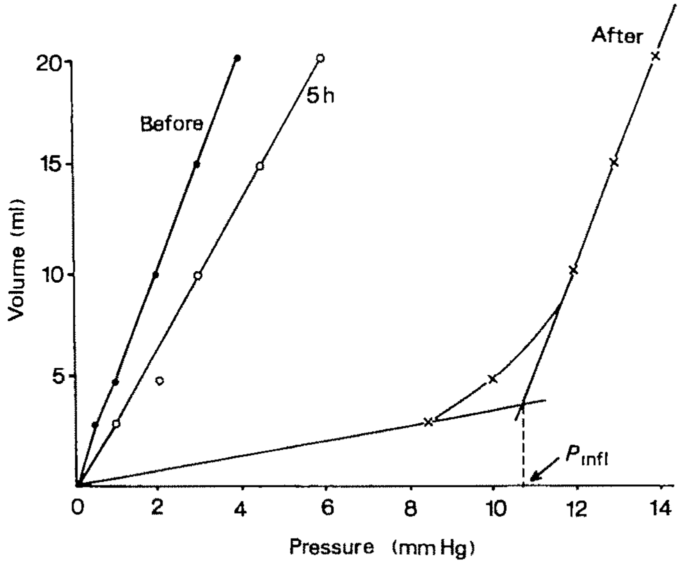

FIG. 3. Inflation pressure–volume curves of one of the animals treated with HFO, before and after lavage and at 5 h. P_{infl} = pressure at the point of inflection of the immediate post-lavage P–V curve

DISCUSSION

The rabbit lung-lavage model was used in this study as it imitates the deficiency of surfactant that is the primary cause of the pathological changes in NRDS. The stability of the model and the similarity of the histological changes to those seen in NRDS have been demonstrated in previous studies [2, 9].

TABLE II. *Mean (SD) of peak and mean airway pressures (Paw), PEEP, and ventilatory rate at each stage of the experiment in the two groups of animals. Significant difference from PEEP*: $^{*}P \leqslant 0.05$; $^{**}P \leqslant 0.001$

Time	Group	Peak *Paw* (mm Hg)	PEEP (mm Hg)	Mean *Paw* (mm Hg)	Vent. rate (b.p.m.)
Pre-lavage	PEEP	9.9 (1.9)	0.25 (0.5)	4.9 (0.8)	24.3 (4.0)
	HFO	9.1 (1.1)	0.4 (0.5)	4.3 (0.4)*	28.9 (0.8)*
Post-lavage	PEEP	17.2 (3.2)	1.8 (0.7)	9.2 (2.1)	26.6 (7.6)
	HFO	15.1 (2.2)*	1.9 (1.1)	8.4 (0.7)*	29.0 (0.9)
1 h	PEEP	23.1 (2.0)	10.3 (1.2)	14.5 (1.1)	36.8 (15.2)
	HFO	16.4 (1.2)**	13.1 (0.8)**	14.8 (0.8)	15 Hz
2 h	PEEP	25.4 (4.6)	10.3 (1.3)	14.7 (1.4)	39.0 (13.6)
	HFO	16.4 (1.6)**	12.4 (1.1)*	14.5 (0.9)	15 Hz
3 h	PEEP	26.9 (3.4)	10.5 (1.1)	14.8 (1.4)	40.1 (12.7)
	HFO	15.8 (1.4)**	12.3 (1.0)*	14.3 (0.8)	15 Hz
4 h	PEEP	25.3 (3.1) ($n = 6$)	10.9 (0.9) ($n = 6$)	14.5 (0.5) ($n = 6$)	43.5 (13.6) ($n = 6$)
	HFO	16.4 (1.3)** ($n = 7$)	12.4 (0.9)* ($n = 7$)	14.2 (0.4) ($n = 7$)	15 Hz
5 h	PEEP	25.5 (0.5) ($n = 6$)	10.9 (0.8) ($n = 6$)	14.6 (0.5) ($n = 6$)	45.2 (14.4) ($n = 6$)
	HFO	16.7 (1.1)* ($n = 5$)	13.0 (1.2)* ($n = 5$)	14.9 (0.2) ($n = 5$)	15 Hz

TABLE III. *Mean (SD) of the static lung compliance below and above the inflection point on the inflation curve and of the end-expiratory lung volume (EELV). Significant difference from PEEP*: $^{*}P \leqslant 0.05$; $^{**}P \leqslant 0.001$

		Compliance (ml mm Hg^{-1})		
Time	Group	Below	Above	EELV (ml)
Pre-lavage	PEEP	—	4.9 (1.0)	—
	HFO	—	5.8 (2.1)	—
Post-lavage	PEEP	0.6 (0.2)	4.2 (2.0)	—
	HFO	0.8 (0.6)	3.9 (1.1)	—
1 h	PEEP	0.7 (0.3)	4.4 (2.4)	33.3 (13.0)
	HFO	2.1 (1.2)* ($n = 6$)	3.8 (1.2) ($n = 6$)	50.4 (7.4)* ($n = 5$)
2 h	PEEP	0.6 (0.2)	3.0 (1.0)	34.9 (12.2)
	HFO	1.6 (1.1)*	3.4 (0.8)	54.6 (12.1)* ($n = 7$)
3 h	PEEP	0.5 (0.2)	3.9 (1.2)	32.7 (9.1)
	HFO	1.8 (1.7)*	4.4 (1.2)	52.9 (9.9)**
4 h	PEEP	0.6 (0.3) ($n = 6$)	4.2 (1.2) ($n = 6$)	36.6 (15.9) ($n = 6$)
	HFO	2.0 (1.2)* ($n = 6$)	4.2 (2.3) ($n = 6$)	52.1 (7.2)* ($n = 7$)
5 h	PEEP	0.5 (0.1) ($n = 5$)	3.7 (1.2) ($n = 6$)	31.7 (19.8) ($n = 6$)
	HFO	1.4 (1.3) ($n = 5$)	4.3 (1.6) ($n = 5$)	53.6 (10.9) ($n = 5$)

TABLE IV. *Hyaline membrane (HM) and neutrophil infiltration (NI) scores (scale 0 = none to 4 = most severe) for the right lungs of the two groups of animals. No significant difference between either the HM or NI scores of the two groups* ($P > 0.05$)

	CMV		HFO	
	HM	NI	HM	NI
	0	4	0	2
	0	3	2	2
	0	3	0	2
	2	4	2	4
	0	1	0	0
	1	1	2	2
	0	1	0	2
	0	4	1	1
Mean (SD)	0.4 (0.7)	2.6 (1.4)	0.9 (1.0)	1.9 (1.1)

Between two and six lung lavages were needed to produce a reduction in arterial oxygen tension to less than 10 kPa. A marked change in the configuration of the P–V curve was observed in all the animals, manifest by the appearance of a clear inflection point. This was situated between airway pressures of 6.2 and 14.0 mm Hg. Below P_{infl}, lung compliance was very low, but above it the compliance was similar to pre-lavage values (table III). The inflection point pressure is believed to represent that at which collapsed alveoli re-open [3, 10]. We have postulated previously that, if surfactant-depleted animals undergo ventilation with CMV with an end-expiratory pressure less than the P_{infl} value (as in CMV), alternate collapse and re-expansion of alveoli occurs during each ventilatory cycle, establishing intra-regional stresses between adjacent, interdependent areas of varying compliance within the lung. This would be expected to damage pulmonary endothelium and epithelium and thus induce hyaline membrane formation. Previous studies by this group comparing the effects of CMV with values of PEEP less than the P_{infl} value and with PEEP equal to P_{infl}, showed that hyaline membrane formation was more severe in the low PEEP group. Similar results were obtained when mean airway pressures were lower in the low PEEP group [9] or were increased to match those in the high PEEP group [2]. These results suggest that the most important factor in minimizing lung damage is the prevention of the cyclical collapse and re-expansion of low compliance areas of the lungs.

Maintenance of lung volume may prevent direct damage to the pulmonary vasculature by minimizing intra-regional stresses, or it may prevent the activation of polymorphonuclear leucocytes [10]. However, no significant quantitative difference in the degree of neutrophil infiltration was demonstrated between the two groups of animals in this experiment. Alternatively, lung volume maintenance may act by reducing regional lung hypoxia, which has been shown to have important metabolic effects within the lung [11]. Another possibility is that maintenance of lung expansion may increase lung surfactant activity. It has been shown previously that the use of PEEP increases surfactant activity by either stimulating the production, or preventing the destruction, of surfactant [12, 13]. An increase in surfactant metabolism has been found in (normal) rabbits during CMV compared with spontaneous breathing [14]. However, a further study by the same group comparing the effects of HFO at a frequency of 5 Hz and *P*aw of 5 cm H_2O with spontaneous breathing revealed that the amount and composition of surfactant phospholipids (both in the lamellar body and in the alveolar lavage) were similar [15].

In the present study, the mean airway pressure was adjusted to 15 mm Hg to match the values used in the previous study, so that the depression of cardiac output would be similar in the two groups. As shown in table I, there were no significant differences in arterio–venous oxygen content difference. However, a number of measurements in the previous study were excluded because of technical difficulties, so that the value of any statistical comparison is limited. The large arterio–venous oxygen content differences in the HFO group suggest that cardiac output was decreased markedly, and this is confirmed by the large base deficit despite bicarbonate infusion.

As the mean *P*aw was the same in the two groups but the amplitude of airway pressure oscillations was less in the HFO group, there was a higher end-expiratory pressure in the HFO group. This, and the probable gas-trapping associated with HFO, resulted in a higher EELV in the HFO group than in the high PEEP group, together with higher Pa_{O_2} values. This suggests that alveolar recruitment continued to occur at airway pressures greater than the inflection point pressure. However, although changes in airway pressure were smaller in the HFO group and peak airway pressures were higher in the CMV group, hyaline membrane formation was not reduced in the HFO group. It is possible that alveolar pressures were greater than airway pressures because of gas trapping during HFO, and that the high pressures resulted in increased lung damage. Intra-regional stresses might also have been generated by variations in regional time constants or by local resonant amplification of the airway pressure variations. Damage might have resulted also from the high accelerations imparted to the gas oscillating up and down the airways during HFO.

In animals subjected to HFO, there was a return towards the normal shape of the P–V curve in five of the eight animals. The inflection point tended to disappear and the initial increment in volume could be injected with a smaller change in pressure. Similar changes were seen in only two of the eight animals in the high PEEP CMV group. The change in shape of the P–V curve suggests that surfactant was being replenished, but that the hyaline membrane formation may have resulted from damage produced in the first 1 or 2 h after lavage.

HFO resulted in a marked improvement in gas exchange compared with high PEEP. This was manifest by significantly greater arterial oxygen tensions throughout the experiment and by enhanced efficiency in removal of carbon dioxide during HFO. Indeed, maintenance of normocapnia proved difficult, becuase of problems in adjustment of tidal volume. We were unable to obtain a leak fine enough to allow small reductions in tidal volume without loss of an adequate PEEP. Others have also demonstrated this increased efficiency of gas exchange during HFO at 15 Hz [1, 16] and high frequency jet ventilation (HFJV) at 4 Hz [17]. Kolton and colleagues [16] used the same rabbit model as was used in these experiments, studying oxygenation during both CMV and HFO in the same animals, with matched mean airway pressures. They found that both Pa_{O_2} and lung volumes were greater with HFO. They suggested that HFO exploits the more favourable deflation limb of the P–V curve, so that constant lung volume is maintained at or near optimal values throughout the ventilatory cycle, resulting in maximal recruitment. They postulated that two other mechanisms may also contribute to improved oxygenation: redistribution of oedema fluid and facilitated diffusion. Using a lower ventilatory frequency of 4 Hz (HFJV) in rabbits, Quan and co-workers [7] also showed improved oxygenation compared with CMV. They suggested that this was a result of increased lung volumes (although they did not measure them). They suggested also that increased airway turbulence might be a factor [7]. Jibelian and co-workers [17], using a dog lung lavage model, compared gas exchange during CMV, CMV with PEEP, high frequency pulse ventilation (HFPV) at 4 Hz and HFPV with PEEP. Oxygenation was improved by HFPV and it was found that the peak airway pressure, rather than the mean, was the more critical determinant of Pa_{O_2}. They ascribed the increase in Pa_{O_2} to a "dynamic PEEP effect" of high frequency ventilation.

However, Truog and colleagues failed to demonstrate any difference in oxygenation at similar mean airway pressures during CMV and HFO, but their CMV animals did develop hypercapnia [6]. The study model was the premature primate. There was also no significant difference in lung volumes and no difference between surface active material concentration with each treatment. The contrast between these findings and those of other experiments, including our own, may result from a difference in either the type of model or the species. Truog suggested that rabbits may have better regional gas distribution because of greater collateral ventilation, that hyaline membrane disease in the primate may have different histological features and that there may be a difference in alveolar surface structure.

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PERCUTANEOUS ANTERIOR APPROACH TO THE COELIAC PLEXUS USING ULTRASOUND

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SUMMARY

A new approach is described to the neurolytic block of the coeliac plexus through the anterior abdominal wall using ultrasonic guidance. In nine patients, ultrasound was used for needle placement and examination of the spread of injection. Total pain relief was obtained in seven of the patients after 2 weeks and in five patients after 6 months. No serious complications were observed. The anterior approach is simple and useful in those patients with chronic pancreatic pain undergoing biopsy of the pancreas, and in those terminally ill or heavily sedated patients who have difficulty in tolerating the prone flexed position.

Coeliac plexus block is an effective method for the relief of pain produced by upper abdominal cancer [1, 2] or chronic pancreatitis [3–5]. The CT guided technique [6–9] allows accurate needle placement for coeliac injection and reduces the risks associated with this procedure. This paper reports our experience using ultrasound for performing percutaneous coeliac plexus block in patients with chronic pancreatic pain.

PATIENTS AND METHODS

We used this technique in nine patients (seven male) aged 44–61 (mean 53.5) yr with upper chronic pancreatic pain produced by pancreatic carcinoma (seven) and chronic pancreatitis (two). In six patients the block was performed at the same time as anterior percutaneous aspiration biopsy of the pancreas. The patients were fasted for at least 12 h before the procedure; no other specific preparation was administered and no prophylactic antibiotics were used.

The block was performed using ultrasound guidance with the patient in the supine position. The coeliac trunk and abdominal aorta were localized by the radiologist. The ultrasound enabled calculation of the distance from the point of entry in the upper abdominal wall to the coeliac trunk, the angle of needle entry and the depth (fig. 1). Mepivacaine 1 % was infiltrated at a point of entry situated 1–2 cm below and to the left of the xiphoid process, perpendicular to the spinous process of the L1 vertebral body. A 22-gauge 15 cm long needle was inserted and its tip positioned over the coeliac plexus in the upper preaortic area. When the correct position was verified with ultrasound (fig. 2), 1 % mepivacaine 20 ml was introduced. If the test with local anaesthetic proved to be positive and the spread of the solution was localized around the aorta at the level of the coeliac trunk predominantly in the preaortic region (fig. 3), the neurolytic solution of 50 % alcohol 35 ml was injected, the spread again being verified by ultrasound (fig. 4).

On completion of the neurolytic block, the radiologist performed aspiration biopsy of the pancreas in six patients. In four of these patients biopsy confirmed the presence of adenocarcinoma of the pancreas. The patient was then taken to the recovery room and monitored for 24 h.

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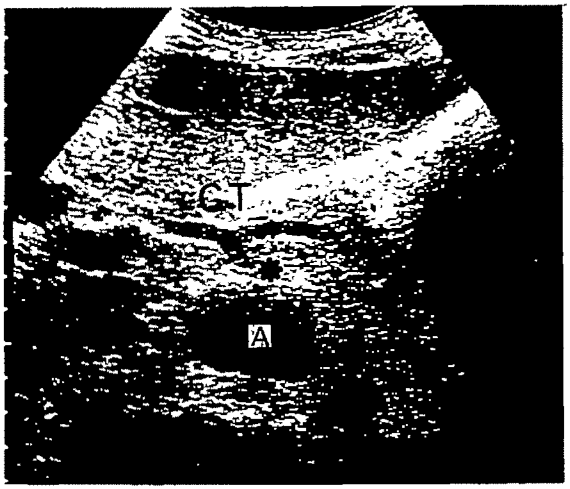

FIG. 1. Transverse ultrasound control showing the abdominal aorta (A) and the coeliac trunk (CT) in the upper preaortic area. Black star indicates the point where the needle tip must be located to perform the block. White scale indicates distance from the abdominal wall to this point.

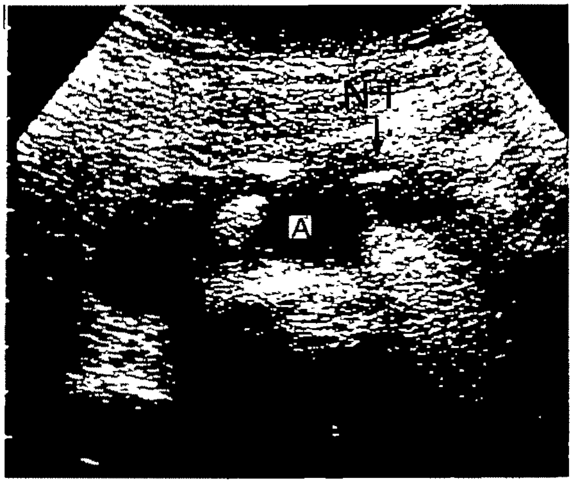

FIG. 2. Transverse echography of the upper abdomen showing the abdominal aorta (A) and the location of the needle tip (NT) in the left upper preaortic area.

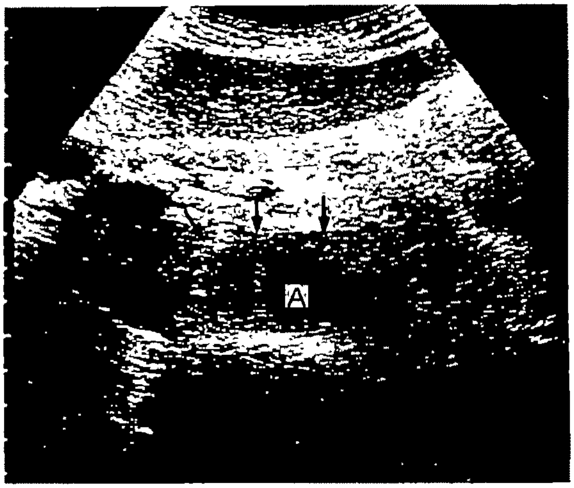

FIG 3 Transverse echography control of the upper abdomen. Arrows indicate a round image that confirms the correct spread of the local anaesthetic around the aorta (A). Local anaesthetics are seen as black images when ultrasound guidance is used.

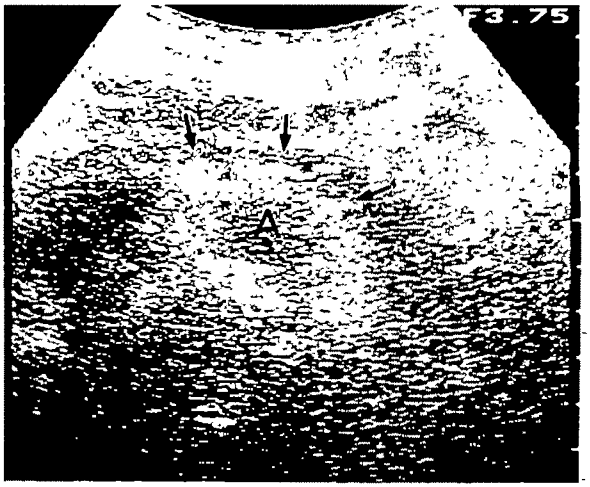

FIG. 4. Transverse echography performed at the level of the coeliac trunk. Arrows indicate spread of the neurolytic agent around the aorta. Alcohol is seen as a white image when ultrasound guidance is used.

RESULTS

Pain relief was assessed 1–2 weeks and 6 months following the neurolytic procedure and scored subjectively by the patient on a 0–4 scale (0 = no pain relief; 4 = total ablation of pain). Patients having pain relief were followed up intermittently over a period of 6 months (table I).

Seven of the nine patients with abnormal pain had total pain relief 2 weeks after the neurolysis and two had no pain relief. After 6 months, five patients continued with total pain relief and did not require analgesic medication; two patients with chronic pancreatitis had moderate pain relief requiring analgesic medication. The two remaining patients had no pain relief, and one died 3 months later.

No serious side effects or complications were encountered in this study. Five patients had local

TABLE I. *Pain relief achieved after anterior percutaneous coeliac plexus block, on a scale from 0 = no pain relief to 4 = total pain relief*

After 2 weeks		After 6 months	
No. patients	Score	No. patients	Score
7	4	5	4
2	0	2	2
		2	0

pain which coincided with the injection of the neurolytic agent. Four patients required an i.v. hypnotic agent. Six patients had increased peristalsis, but this did not last more than 48–72 h.

DISCUSSION

Coeliac plexus block using landmarks without CT or ultrasound guidance have been reported to have numerous complications [10–12]. The use of these techniques ensures a more efficient and safe procedure. The CT provides a better quality image than ultrasound, but is costly and time consuming, whereas ultrasound guidance is quicker and more economical [13, 14]. Another advantage is that no contrast medium is required and only one needle is needed.

The anterior approach to percutaneous coeliac plexus block may be used for those patients with chronic abdominal pain undergoing percutaneous visceral biopsy using ultrasound guidance; those terminally ill patients who are unable to tolerate the prone, flexed position; and those who require meticulous monitoring and good ventilation [15, 16]. The anterior abdominal approach with ultrasound guidance allows the patients to remain supine.

The success rates of the intraoperative technique are not superior to those obtained using the percutaneous techniques [17, 18]. The reported cases of incomplete pain relief may be related to spread of the injected alcohol in such a way that it is "lost" into the operative field, while percutaneously injected alcohol remains localized in the tissue planes [19]. In order to avoid complications from visceral perforation it is necessary to use a fine, 22-gauge needle [20, 21]. The development of a pancreatic fistula is more common when biopsies are performed with an 18-gauge needle than with a finer needle [22]. This complication is usually caused by the biopsy rather than by the coeliac plexus block. The complications of this technique are surprisingly low if one considers that the needle may pass through the stomach, intestine and pancreas [23].

As pain relief is subjective, it is difficult to quantify the degree of success in relieving abdominal pain with neurolytic techniques. However, our results are similar to those obtained by other techniques [24].

The spread obtained using the anterior approach covers the coeliac plexus without involving the retrocrural region and the psoas compartment containing the sympathetic chain and lumbar plexus. This reduces the risk of neurological complications.

Because of anatomical variations in the coeliac plexus [25], CT and ultrasound guidance are the only methods capable of demonstrating accurately the location of the needle in relation to the coeliac trunk and the spread of the neurolytic agent around the aorta following injection.

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CONTROLLED TRIAL OF EXTRADURAL BUPIVACAINE WITH FENTANYL, MORPHINE OR PLACEBO FOR PAIN RELIEF IN LABOUR

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SUMMARY

In a prospective, randomized double-blind study carried out on 255 parturients, fentanyl 80 µg (n = 81), morphine 4 mg (n = 83) or placebo (n = 85) was added to 0.25% bupivacaine administered extradurally for pain relief during labour. Fentanyl increased the mean duration of bupivacaine analgesia by 30% and did not reduce the rate of inadequate pain relief. Morphine did not increase the mean duration of bupivacaine analgesia significantly, but increased the rate of inadequate pain relief. It was concluded that morphine 4 mg added to extradural 0.25% bupivacaine was of no value.

The use of extradural opioids for pain relief in labour has been shown to be inefficient and hazardous [1–9]. It has been demonstrated, however, that the combination of an opioid and a local anaesthetic may improve both the onset and the duration of analgesia produced by the latter, and provide better quality of analgesia [10–13].

Niv and co-workers concluded that the concomitant use of extradural morphine 2 mg augmented the analgesic effect of 0.25% bupivacaine [12], but Cohen and colleagues found that the addition of extradural fentanyl 50 or 100 µg to 0.25% bupivacaine 9 ml did not result in significant improvement in analgesia compared with the local anaesthetic alone [14]. The majority of clinical trials have been limited to small numbers of parturients, and none has compared fentanyl with morphine in combination with extradural bupivacaine. This study has been carried out in a prospective, randomized double-blind manner to compare, in a large study, the efficacy of extradural combinations of fentanyl with bupivacaine, morphine with bupivacaine and placebo with bupivacaine for control of labour pain.

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee and informed consent was obtained from all participating patients—255 healthy pregnant women with uncomplicated full-term gestation (> 38 week) who elected to have extradural analgesia for labour and delivery. All patients were in labour with a healthy singleton fetus in a cephalic presentation. Previous opioid administration excluded the patient from the study.

When a patient requested pain relief, an extradural catheter was inserted at the L2/3 or L3/4 space via a 17-gauge Tuohy needle. A 4-ml test dose of 0.25% plain bupivacaine was injected. Patients were allocated randomly to one of the three groups. The ampoules of extradural solution had been coded randomly and prepared by the hospital pharmacy. Each ampoule contained 8 ml of 5% dextrose alone or in combination with either fentanyl 80 µg or 4 mg of preservative-free morphine hydrochloride. The pH values of the three solutions were, respectively, 4.46 (placebo), 4.83 (fentanyl) and 4.60 (morphine). The contents of the coded ampoule were administered extradurally 7 min after the test dose. Twelve minutes after the test dose, each parturient was given 0.25% plain bupivacaine 8 ml. This timing was chosen to avoid dilution of bupivacaine. The

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TABLE I. *Maternal characteristics and state of cervical dilatation at the onset of the study (mean (SEM)). No significant differences*

	Placebo group ($n = 85$)	Fentanyl group ($n = 81$)	Morphine group ($n = 83$)
Age (yr)	29.3 (0.6)	29.7 (0.6)	28.8 (0.7)
Weight (kg)			
Before pregnancy	55.9 (0.9)	57.1 (1.0)	53.7 (1.7)
At term	69.6 (1.3)	69.2 (1.7)	69.8 (1.8)
Height (cm)	163.0 (0.7)	164.0 (0.8)	157.0 (6.4)
Parity			
Primiparous	57	53	58
Multiparous	28	28	25
Term (week)	39.6 (0.1)	39.7 (0.1)	39.7 (0.1)
Cervical dilatation (cm)	3.3 (0.1)	3.4 (0.1)	3.3 (0.1)

duration of analgesia was defined as the time between administration of the test dose and the first request for re-injection.

The patients were asked to rate the efficacy of the extradural block. Analgesia was considered successful and adequate when contractions were painless. Inadequate pain relief was assessed as decreased but persisting painful contractions, persisting painful area or lateralized analgesia. When a further injection was needed within 35 min, patients were excluded from data analysis. Subsequently, 0.25% bupivacaine was administered extradurally at the patient's request. Throughout labour, fetal status was assessed by continuous fetal heart rate monitoring. The presence of adverse side-effects was also recorded, including pruritus, nausea and vomiting, drowsiness, hypotension (decrease in systolic arterial pressure of more than 20%), respiratory depression (ventilatory rate less than 10 b.p.m.). The study was terminated at the first reinjection.

All the results are presented as mean (SEM). Statistical analysis was performed using one-way analysis of variance, unpaired Student's t test and Chi-square test, as appropriate. Statistical significance was assumed when $P < 0.05$.

RESULTS

Two hundred and fifty-five women entered the study, but six coded ampoules were opened and not used. Thus data were obtained in 249 parturients allocated randomly to one of the three groups: placebo ($n = 85$), fentanyl ($n = 81$) and morphine ($n = 83$). The three groups were comparable with regard to age, weight, height, parity, term and cervical dilatation at the time of the test dose (table I).

Duration of analgesia. The mean duration of pain relief induced by bupivacaine was significantly greater in the group given fentanyl 80 µg than after placebo (table II). In addition, significantly more parturients were delivered vaginally without an additional dose of bupivacaine (table III). The time elapsed between test dose and delivery was not significantly different in these two groups (115 min *v.* 102 min). In the group given morphine the mean duration of pain relief induced by bupivacaine was not significantly longer than that in the placebo group. The number of parturients delivered vaginally without additional bupivacaine was not different in the morphine and placebo groups (table III). For the

TABLE II. *Mean duration of analgesia assessed as the interval between the test dose and first increment (mean (SEM)).* *$P < 0.05$ *compared with placebo No other significant differences*

	Placebo group ($n = 85$)	Fentanyl group ($n = 81$)	Morphine group ($n = 83$)
Parturients who required an increment	68 (80%)	48 (54.2%)	67 (80.7%)
Duration of analgesia (min)	97.2 (3.7)	132.5 (5.0)*	109.6 (6.4)

TABLE III *Parturients delivered vaginally without a further dose of bupivacaine. The data from five parturients in the fentanyl group who progressed to Caesarean section before an increment was needed are not included in this table.* *P < *0.05 compared with placebo*

	Placebo group (n = 85)	Fentanyl group (n = 81)	Morphine group (n = 83)
Number	17 (20%)	28 (34.5%)	16 (19.3%)
Time elapsed between test dose and delivery (min)	102.5 (9.5)	115.7 (9.5)	92.3 (9.9)

TABLE IV. *Frequency of inadequate pain relief.* *P <*0.05 compared with placebo and fentanyl groups*

	Placebo group (n = 85)	Fentanyl group (n = 81)	Morphine group (n = 83)
Persisting painful contraction	11 (13%)	5 (6.2%)	23 (27.7%)*
Residual painful area	4 (4.7%)	4 (4.9%)	12 (14.4%)*
Lateralized analgesia	4 (4.7%)	0	4 (4.8%)

TABLE V. *Frequency of side-effects* *P < *0.01 compared with placebo group*

	Placebo group (n = 85)	Fentanyl group (n = 81)	Morphine group (n = 83)
Itching	1 (1.2%)	22 (27.2%)*	20 (24%)*
Nausea and vomiting	11 (13%)	6 (7.4%)	27 (32.5%)
Drowsiness	1 (1.2%)	11 (13.6%)*	12 (14.4%)*
Hypotension	2 (2.4%)	4 (4.9%)	3 (3.6%)
Urinary retention	1 (1.2%)	2 (2.4%)	5 (6%)

parturients who were delivered without additional bupivacaine, the time elapsed between the test dose and delivery was not significantly different (92 min *v.* 102 min). There was no significant difference in duration of pain relief in the morphine and fentanyl groups (table II).

Efficacy of analgesia. There was an equal rate of inadequate pain relief (persisting painful contraction or painful area) in the fentanyl and placebo groups (table IV). However, there was a greater rate of inadequate pain relief in the morphine group, compared with the fentanyl and placebo groups (table IV).

Side effects. There was a higher rate of side effects in the fentanyl and morphine groups than in the placebo group (table V). In both opioid groups the frequency of pruritus and drowsiness was greater than in the placebo group (table V). One patient with drowsiness in the morphine group required repeated administration of naloxone.

Mode of delivery and Apgar scores. Sixty-eight percent of patients had a normal vaginal delivery, 8% had Caesarean section and 24% had forceps delivery; there was no significant difference between the three groups. No changes in fetal heart pattern occurred in association with the extradural blocks. Apgar scores > 7 at 1 min and > 9 at 5 min were achieved in 94.8% and 98.4% of neonates, respectively, with no significant difference between the three groups.

DISCUSSION

In non-pregnant patients, extradural fentanyl produces a short lasting analgesic effect of rapid onset [15]. In pregnant patients, extradural fentanyl has been shown to be effective only in achieving pain relief in the first stage of labour [4, 16, 17]. Several investigators [4, 10, 11, 13] reported that the combination of fentanyl with small doses of bupivacaine increased the duration of analgesia provided by bupivacaine alone administered extradurally. However, in a recent study [14] the addition of fentanyl 50 or 100 μg to 9 ml of 0.25% extradural bupivacaine following a test dose of 1% lignocaine 3 ml was not found to prolong analgesia. In our study, the addition of fentanyl 80 μg to 0.25% bupivacaine 8 ml after a test dose of 0.25% bupivacaine 4 ml was found to increase significantly the duration of analgesia produced by bupivacaine. Our study confirmed the observations of Cohen [14] that the combination did not increase the success rate of complete analgesia produced by bupivacaine. In addition, no clinical respiratory depression was reported with the fentanyl combination.

In non-pregnant women, extradural morphine alone provides a long-lasting analgesia of slow onset. In pregnant women, extradural morphine alone, in a dose of 5 mg or less, is ineffective in providing satisfactory pain relief throughout labour [1, 3, 5–9], probably because the extradural vascular congestion of pregnancy enhances vascular absorption of morphine [18–24]. Several investigators have reported that extradural bupivacaine improves the quality of analgesia when administered after [9] or simultaneously with [12] extradural morphine during the first stage of labour. However, in our double-blind study we could not demonstrate any improvement in analgesia by combining morphine with bupivacaine.

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AWARENESS FOLLOWING DIFFERENT TECHNIQUES OF GENERAL ANAESTHESIA FOR CAESAREAN SECTION

A. BARAKA, F. LOUIS, R. NOUEIHID, M. DIAB, A. DABBOUS AND A. SIBAI

SUMMARY

Using the isolated arm technique, the frequency of awareness was evaluated in 50 full-term patients undergoing elective Caesarean section under general anaesthesia. In 20 patients, anaesthesia was induced with thiopentone 4 mg kg^{-1}, and in the other 30 patients, induction was with ketamine 1.5 mg kg^{-1}. Following suxamethonium 1.5 mg kg^{-1} and tracheal intubation, anaesthesia was supplemented during the induction–delivery period in the thiopentone group with 50% nitrous oxide and 0.5% halothane in oxygen in 10 patients, and with 1% halothane in 100% oxygen in the other 10 patients. In the ketamine group, the patients underwent ventilation with 50% nitrous oxide and 0.5% halothane in oxygen in 10 patients, with 1% halothane in 100% in 10 patients, and with 100% oxygen only in the last 10 patients. Awareness was significantly greater after induction with thiopentone (14/20) than after ketamine (4/30). There were no significant differences in Apgar scores or umbilical vein blood-gas values in the newborns.

Awareness during general anaesthesia in patients undergoing Caesarean section may be a harrowing experience [1]. The incidence of awareness during Caesarean section is high during thiopentone–nitrous oxide–oxygen anaesthesia [2]. The addition of 0.5% halothane has been suggested to decrease the incidence of awareness [3,4]. We have examined the incidence of awareness in patients undergoing Caesarean section, compared with other techniques of general anaesthesia.

PATIENTS AND METHODS

We studied 50 full-term healthy patients undergoing elective Caesarean section (mean age 31 (SD 4.9) yr, mean weight 71 (SD 8.3) kg). Patients with a history of hypertension or pre-eclampsia and those with signs of fetal abnormality or distress were excluded from the study.

The 50 patients were allocated randomly to five equal groups. In group I, anaesthesia was induced with thiopentone 4 mg kg^{-1}, followed by suxamethonium 1.5 mg kg^{-1} and tracheal intubation. Anaesthesia was supplemented during the induction–delivery time (7.6 (1.4) min) with 50% nitrous oxide and 0.5% halothane in oxygen. In group II, anaesthesia was induced with thiopentone 4 mg kg^{-1} and suxamethonium 1.5 mg kg^{-1}, and supplemented during the induction–delivery time (7.0 (1.2) min) with 1% halothane in oxygen. In group III, anaesthesia was induced with ketamine 1.5 mg kg^{-1} and suxamethonium 1.5 mg kg^{-1}, and was supplemented during the induction–delivery time (5.8 (1.5) min) with 50% nitrous oxide and 0.5% halothane in oxygen. In group IV, anaesthesia was induced with ketamine 1.5 mg kg^{-1} and suxamethonium 1.5 mg kg^{-1}, and was supplemented during the induction–delivery time (6.6 (1.9) min) with 1% halothane in oxygen. In group V, anaesthesia was induced with ketamine 1.5 mg kg^{-1} and suxamethonium 1.5 mg kg^{-1}, and the patients underwent ventilation during the induction–delivery time (7.4 (2.7) min) with 100% oxygen without any inhalation anaesthetic supplementation.

All patients were premedicated with glycopyrrolate 0.2 mg i.m. 45 min before surgery. In the operating room, the patient was positioned on

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the operating table with a left lateral tilt of approximately 15°. An i.v. infusion of lactated Ringer's solution was started for fluid and drug administration. Preoxygenation was undertaken with 100% oxygen by facemask.

In all patients, the calculated induction dose of thiopentone (4 mg kg^{-1}) or ketamine (1.5 mg kg^{-1}) was injected rapidly into the i.v. infusion. The patient was then asked to count out aloud or to answer simple questions. When the patient had obviously lost consciousness, suxamethonium 1.5 mg kg^{-1} was given i.v. and the trachea intubated. The interval from the time of injection of the induction agent to administration of suxamethonium was 30–45 s in the thiopentone groups, and 45–90 s in the ketamine groups. Following tracheal intubation, the lungs were ventilated during the induction–delivery period, according to the assigned regimen. After delivery, an arterial blood sample was taken for blood-gas analysis, and anaesthesia was maintained in all patients using 66% nitrous oxide in oxygen, supplemented by fentanyl 3 μg kg^{-1} and alcuronium 0.25 mg kg^{-1}.

Awareness following induction of anaesthesia was detected using the isolated forearm technique [5]. The test was explained clearly to patients before induction. After unconsciousness was produced by ketamine or thiopentone and before suxamethonium was injected, a tourniquet was inflated rapidly to 250 mm Hg in order to maintain motor power in the isolated arm. Following tracheal intubation, the patient's right hand was clasped by the anaesthetist and the patient was asked to squeeze and relax her hand three times successively. The time from injection of the induction agent and testing for awareness was 2–3 min. The test was repeated at 1-min intervals until the baby was delivered. Because hand movement may occur spontaneously or as a response to surgical stimulation, the test was considered positive only if the patient squeezed and relaxed her hand according to instructions.

In all patients, systemic arterial pressure and heart rate were measured before induction, 1 min after induction and before delivery. Immediately after delivery of the baby, blood samples were taken from the radial artery of the mother and umbilical vein of the newborn. Apgar score of the newborn was assessed at 1 and 5 min. Approximate blood loss was estimated in each patient by measuring the amount of blood in the suction bottle and on surgical pads. Following recovery from anaesthesia, and on the next day, the patients were interviewed to assess recall, dreams and hallucinations.

All data (except the frequency data) are means (SD). Frequency data among different groups were compared by Chi-square tests. Analysis of variance (ANOVA) was used to compare data between different groups, and Student's t test was used to compare data within the same group. $P < 0.05$ was considered significant.

RESULTS

Awareness was significantly higher after induction with thiopentone (group I and II) than after ketamine (group III–V) ($P < 0.05$) (table I). The test was positive in 14 of the 20 patients in the thiopentone group. In contrast, only four of the 30 patients in the ketamine group had a positive test. However, the frequencies of recall, dreams and hallucinations were not different. Two of the 20 thiopentone patients had recall, confined to the time of delivery. In the ketamine groups, no patient had recall, but one patient reported pleasant dreams and a second, hallucination.

Control arterial pressure and heart rate before induction were not significantly different between groups (table II). Following induction of anaesthesia and tracheal intubation, heart rate and arterial pressure increased in all groups ($P < 0.05$). The increase in pressure following induction was significantly higher after induction with ketamine than after thiopentone ($P < 0.05$) (table II).

Apgar scores of the newborns at 1 min and 5 min were not significantly different among the

TABLE I. *Incidence of awareness, recall and hallucinations in the five groups*

	Group I	Group II	Group III	Group IV	Group V
Awareness	6	8	1	3	0
Recall	1	1	0	0	0
Dreams	0	0	0	1	0
Hallucination	0	0	1	0	0

TABLE II. *Cardiovascular variables in the five groups of patients*

	Control			1 min after induction			Before delivery		
	SAP (mm Hg)	DAP (mm Hg)	HR (beat min^{-1})	SAP (mm Hg)	DAP (mm Hg)	HR (beat min^{-1})	SAP (mm Hg)	DAP (mm Hg)	HR (beat min^{-1})
Group I	120.9	74.6	85.4	133.7	80	99.1	136.4	80.9	105
	(24.6)	(10.3)	(10.1)	(25.3)	(10)	(16.5)	(16.8)	(7)	(14.7)
Group II	118	74	71	125	77.2	103	131.1	76.5	115
	(9.18)	(6.9)	(29 9)	(14.3)	(4.7)	(5.0)	(23.8)	(8.1)	(20 2)
Group III	121.2	77.5	83.1	147.5	83.7	100	148.7	83.7	106
	(8.3)	(4.6)	(12.1)	(20.5)	(7.4)	(10.8)	(16 4)	(5.17)	(10.8)
Group IV	121	75	84.5	148	84	109	141	84	107
	(11)	(7.07)	(13.4)	(13.2)	(6.9)	(22.3)	(17.9)	(5.2)	(25.8)
Group V	106.3	75.5	91	156	93	111	150	93	133
	(35.6)	(6.8)	(9.6)	(15.7)	(8.2)	(13.4)	(13.3)	(6.7)	(15.3)

TABLE III. *Apgar scores in babies in the five maternal groups*

Apgar score < 7	Group I	Group II	Group III	Group IV	Group V
1 min	0/10	0/10	1/10	2/10	1/10
5 min	0/10	0/10	0/10	0/10	0/10

TABLE IV. *Oxygen and carbon dioxide tensions in maternal arterial blood and umbilical vein blood*

	Group I	Group II	Group III	Group IV	Group V
Maternal artery					
$P\mathrm{O}_2$ (kPa)	33.2 (12.2)	48.8 (10.9)	32.8 (11.2)	54.4 (16.1)	50.3 (15.9)
$P\mathrm{CO}_2$ (kPa)	4.9 (0.9)	4.9 (0.6)	5.1 (0.7)	4.9 (0 7)	5.0 (0.8)
Umbilical vein					
$P\mathrm{O}_2$ (kPa)	4.9 (0.7)	5.3 (0.7)	4.1 (0.7)	5.3 (1.4)	4.2 (0 8)
$P\mathrm{CO}_2$ (kPa)	6.1 (0.6)	5.8 (0.9)	6.3 (0.6)	5.9 (1.5)	5.7 (0.9)

different groups. None of the newborns needed any unusual resuscitative measures, and all newborns scored more than 7 at 5 min (table III).

Umbilical vein $P\mathrm{CO}_2$ was not significantly different between groups, and was always higher than the corresponding maternal $P\mathrm{CO}_2$ (table IV). Also, the umbilical vein $P\mathrm{O}_2$ was not significantly different between the five groups, and was not significantly greater when the mother received 100% instead of 50% oxygen.

Uterine tone and bleeding were acceptable to the surgeon. There was no obvious difference in estimated blood loss between groups. Approximate blood loss was 563 (195) ml in group I, 495 (158) ml in group II, 685 (69) ml in group III, 485 (170) ml in group IV and 466 (146) ml in group V.

DISCUSSION

General anaesthesia for patients undergoing Caesarean section should ensure unconsciousness in the mother, while minimizing anaesthetic-related depression of the infant [4]. Induction with a sleep dose of thiopentone and maintenance with nitrous oxide in oxygen is associated with a high incidence of awareness [1,2]. The addition of 0.5% halothane to supplement nitrous oxide in oxygen anaesthesia has been shown to prevent maternal awareness without adverse effects on the neonate [3,4]. However, the present study using the isolated forearm technique has shown that the incidence of awareness following thiopentone induction is high, when anaesthesia is maintained with 50% nitrous oxide and 0.5% halothane in oxygen or with 1% halothane in 100% oxygen.

Crawford suggested that patients who show awareness rapidly after induction of anaesthesia may never have lost consciousness following administration of a "standard dose" of induction agent, and stressed that care be taken to ensure that the patient is unconscious before administration of a neuromuscular blocking drug [6]. In the present report, suxamethonium was administered only when the patient obviously lost consciousness following the injection of thiopentone or ketamine.

The high frequency of awareness in our study following a sleep dose of thiopentone may be attributed to its rapid redistribution, with rapid recovery of consciousness in the non-premedicated patients. However, only two of the 14 patients with awareness had recall of the intraoperative events. Recall was confined to the time of delivery. Awareness and recall are related only partly because awareness may occur without recall [7]. Awareness under general anaesthesia, even without recall, may result in postoperative neurosis marked by anxiety, irritability, repetitive nightmares and preoccupation with death [8, 9].

In contrast with the thiopentone groups, awareness occurred in only four of the 30 patients in whom induction was with ketamine. Our results support earlier findings that ketamine 1.0 mg kg^{-1} blocked maternal responsiveness to commands more effectively after anaesthetic induction for Caesarean section than did thiopentone 4 mg kg^{-1} or a combination of thiopentone and ketamine in lower dose [10]. In our study, hallucinations were observed only in one patient of the ketamine group and a second patient reported pleasant dreams, suggesting that hallucinations and other related phenomena associated with ketamine may be low in obstetric patients.

In all groups, heart rate and arterial pressure increased moderately following induction of anaesthesia and tracheal intubation. The increase in pressure was significantly higher in patients who received ketamine than in the patients given thiopentone. This may be attributed to the sympathomimetic effect of ketamine [11]. Thus ketamine must not be used in patients with a history of hypertension or pre-eclampsia.

There was no significant difference in Apgar scores or umbilical vein blood-gas values of the newborns in the five groups. The umbilical vein $P\text{O}_2$ was not significantly greater in mothers receiving 100% oxygen compared with 50%. This finding supports our previous study which demonstrated that fetal $P\text{O}_2$ correlates with maternal Pa_{O_2} within the range 10.5–26.7 kPa, but does not increase further with additional increases in maternal $P\text{O}_2$ [12]. Although the use of 100% oxygen had no significant effect on umbilical vein $P\text{O}_2$ compared with 50% oxygen in this study, the higher maternal $F\text{I}_{\text{O}_2}$ may be beneficial for a fetus suffering from intrauterine asphyxia [13]. Also, avoidance of nitrous oxide obviates its uptake by the fetus *in utero* [14], and hence can prevent diffusion hypoxia in the newborn when it commences breathing [15].

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NEUROBEHAVIOURAL EFFECTS OF PROPOFOL ON THE NEONATE FOLLOWING ELECTIVE CAESAREAN SECTION

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SUMMARY

Forty mothers undergoing elective Caesarean section under general anaesthesia were allocated randomly to receive either propofol 2.8 mg kg^{-1} (n = 20) or thiopentone 5 mg kg^{-1} (n = 20) for induction of anaesthesia. Twenty neonates delivered by uncomplicated vaginal delivery were evaluated also as unmedicated controls. Neurobehavioural examinations were carried out at 1, 4 and 24 h after delivery. Infants in the propofol group had lower Apgar scores at 1 and 5 min; 25% of them had muscular hypotonus at 5 min. This hypotonus was not noted during the Early Neonatal Neurobehavioural Scale (ENNS) examination. Newborn children examined 1 h after birth, after maternal anaesthesia with propofol, showed a depression in alert state, pinprick and placing reflexes, and mean decremental count in Moro and light. There was a generalized irritability in 25% of them. This depression was not observed at 4 h.

There are few studies of the neonatal effects of propofol when given as an induction agent for Caesarean section. Although propofol has been reported to produce ventilatory depression [1], in a pilot study Couper and Lombard [2] did not observe adverse neonatal effects (evaluated by Apgar score) after a single bolus of 2.5 mg kg^{-1} administered for elective Caesarean section. After a single bolus dose of propofol, a maternal:fetal plasma concentration ratio of 0.70 was found [3] (less than that reported for thiopentone [4]), and the mean UA:UV ratio at delivery indicated complete distribution throughout the fetus and a relatively rapid equilibration of propofol. In this study [3], 70% of neonates showed an Amiel-Tison's score [5] of less than 35 at 30 min after delivery. This depression was not present at 2 and 24 h; however, the study was limited by lack of control data.

The purpose of the present study was to evaluate the neonatal neurobehavioural effects of propofol used as an induction agent for general anaesthesia for elective Caesarean section.

PATIENTS AND METHODS

The Early Neonatal Neurobehavioural Scale (ENNS) [6] was administered to 60 neonates in a study approved by the local Human Investigation Committee. Informed consent was obtained from all mothers. Forty mothers undergoing elective Caesarean section under general anaesthesia were allocated randomly to receive either propofol 2.8 mg/kg pregnant body weight (PBW) (study group, 20 patients) or thiopentone 5 mg/kg PBW (control group, 20 patients) for induction of anaesthesia. A third group of 20 neonates (unmedicated control group), delivered by uncomplicated, spontaneous vaginal delivery without analgesia, was evaluated also as a control group.

All mothers were at term (gestational age 38–41 weeks), with a single fetus and uncomplicated pregnancy. Gestational age was estimated using the first day of the last menstrual period and confirmed by ultrasound analysis. Mothers who gave birth spontaneously had a comparable duration of labour.

General anaesthesia for Caesarean section was standardized with the patient in a 15° left lateral tilt and comprised preoxygenation, followed by

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the induction agent and suxamethonium 1 mg/kg PBW, tracheal intubation and ventilation of the lungs with 50% nitrous oxide in oxygen until delivery. No volatile agent was given. Neuromuscular block was provided by intermittent doses of suxamethonium. After delivery, anaesthesia was deepened with fentanyl and droperidol or a volatile agent.

Neonates were evaluated by Apgar scoring at 1 and 5 min, by an independent observer. The neurobehavioural examination was performed at 1, 4 and 24 h after delivery, the 24-h examinations midway between feeds. All neonates were assessed in the same environmental conditions, and the examiners were unaware of the group to which the infant belonged.

The ENNS includes 11 individual observations of primary reflexes, muscle tone and decrement response to stimulation, each measured on a four-point ordinal scale, observations on states of consciousness and one general assessment of the infant's neurobehavioural state. State of consciousness is recorded before each individual test. In accordance with previous studies [7, 8], six states of consciousness are recognized: two sleep states: light sleep (S1) and deep sleep (S2); and four awake states: drowsy state (A1), fussing state (A2), alert inactivity (A3) and crying (A4). In this study, because the infant's state was modified by the stimuli given, the infant's spontaneous state observed in the 2 min immediately before stimulation was recorded also, as the "initial state".

In accordance with Scanlon's neurobehavioural test [6], the four tests for muscle tone (pull to sitting, arm recoil, truncal tone and general body tone) were scored: 0–1 = absent or mediocre response, 2 = normal response, 3 = hypertonicity (which is presumed to be abnormal). Tests for four primary reflexes (rooting, sucking, placing reactions and Moro), responsiveness to external stimuli (pinprick and sound) and overall alertness were recorded 0 = absent, 1 = weak or delayed, 2 = intermediate or normal, 3 = strong. The neonate's ability to react appropriately to repetitive stimuli (habituation) was evaluated by the response decrement to repeated pinprick of the sole of the foot, Moro manoeuvre, light stimulus to the eyes and the sound of a bell. The response decrement was measured by counting the number of stimuli required before a change occurred in the infant's initial best response.

The total doses of thiopentone and propofol used were also noted.

Statistical analysis of neonatal scores was performed by Mann–Whitney U test. Differences were considered significant in the two-tailed test when P was 0.05 or less. Student's t test was used for parametric data. $P \leqslant 0.05$ was considered significant.

TABLE I. *Details of patients studied* (n = *20 for each group*). *Maternal data: mean* (*SD*) *age, weight, height, parity and fetal presentation. Neonatal data: mean* (*SD*) *weight, height and sex; mean I–D and U–D intervals. No statistical differences between the groups* (*Student's* t *test*)

	Spontaneous delivery group	Thiopentone group	Propofol group
Mother			
Age (yr)	30.5 (2.8)	30.9 (5.5)	30.9 (4.5)
Weight (kg)	67.3 (7.4)	69.6 (6.2)	69.7 (9.1)
Gestational age (weeks)	39.2 (1.0)	40.1 (0.5)	39.6 (0.4)
Primiparous	7	7	7
Multiparous	13	13	13
Fetal presentation			
Vertex	18	18	17
Breech	2	2	2
Other	—	—	1
Neonate			
Weight (g)	3424.5 (377.9)	3412.5 (368.7)	3326.0 (457.6)
Height (cm)	50 4 (1.8)	51.1 (2.8)	50.6 (2.2)
Sex (M/F)	(11/9)	(12/8)	(13/7)
I–D interval (min)	—	10.8 (3.5)	11.0 (3.9)
U–D interval (s)	—	61.0 (36.7)	58.3 (30.8)

TABLE II. *Apgar scores at 1 and 5 min* (n = *20 for each group*). *Scores in the thiopentone group are significantly different from those of the spontaneous delivery* (P < 0 002) *and propofol* (P < *0.05*) *groups at 1 and 5 min. Scores in the propofol group significantly different from those of the spontaneous delivery group at 1 min* (P < *0.002*) *and at 5 min* (P < *0.02*) (*Mann–Whitney* U *test*)

Apgar score	Spontaneous delivery group	Thiopentone group	Propofol group
1 min			
7	—	—	2
7	—	5	8
8	—	6	7
9	20	9	3
10	—	—	—
5 min			
7	—	—	—
7	—	—	1
8	—	3	3
9	—	6	10
10	20	11	6

RESULTS

All mothers were comparable for age, weight, height, gestational age, parity and fetal presentation. All the neonates were comparable for age, weight, height and sex. There were no significant differences in induction to delivery (I–D) and uterine incision to delivery (U–D) intervals between the groups (table I). The mean total doses of thiopentone and propofol given for induction of anaesthesia were 361 (40.8) mg and 192 (14.9) mg, respectively.

TABLE III. *Mean (SD) number of changes in labile state of infant during the examination in the spontaneous delivery, thiopentone and propofol groups at 1, 4 and 24 h of life* (n = 20 *infants for each group*). **Significantly different* ($P < 0.02$) *compared with spontaneous delivery group and* ($P < 0.01$) *thiopentone group* (*Student's* t *test*)

Group	1 h	4 h	24 h
Spontaneous delivery	2.9 (1.1)	2.8 (1.1)	2.4 (1.2)
Thiopentone	2.3 (1 4)	2 2 (1.2)	2.6 (1 2)
Propofol	2.5 (1.1)	3.0 (1.2)	1.6 (1 4)*

Infants in the propofol group had lower Apgar scores than those in the thiopentone and spontaneous delivery groups (table II). These differences were significant both at 1 and at 5 min. In no case was the lower Apgar score a result of a low score for heart rate or ventilation. Five neonates in the propofol group had profound hypotonus at birth and one neonate was somnolent. Only one

TABLE IV. *ENNS scores at 1, 4 and 24 h of life* (n = 20 *for each group*). *S = Spontaneous delivery group; T = thiopentone group; P = propofol group. Significant differences*. ***$P < 0.002$ v. *thiopentone group and* $P < 0.02$ v. *spontaneous delivery group at 1 h;* *$P < 0.05$ v. *thiopentone group at 1 h;* †$P < 0.05$ v. *spontaneous delivery group at 4 h;* §$P < 0.05$ v. *thiopentone and spontaneous delivery groups at 1 h;* **$P < 0.02$ v. *thiopentone group and* $P < 0.002$ v. *spontaneous delivery group at 1 h*

		Score at 1 h				Score at 4 h				Score at 24 h			
	Group	0	1	2	3	0	1	2	3	0	1	2	3
Pin-prick	S	—	8	11	1	—	7	12	1	—	3	16	1
	T	—	4	15	1	—	6	12	2	—	4	12	4
	P***	2	16	2	—	—	11	9	—	—	8	12	—
Pull to sitting	S	2	12	6	—	2	7	11	—	—	6	12	2
	T	3	9	7	1	3	5	11	1	—	5	14	1
	P	3	10	7	—	3	6	10	1	1	3	16	—
Arm recoil	S	—	10	8	2	1	5	14	—	—	9	11	—
	T	—	6	13	1	—	11	9	—	1	9	9	1
	P	1	10	7	2	1	9	9	1	1	11	8	—
Truncal tone	S	1	11	8	—	1	7	12	—	—	7	11	2
	T	2	9	9	—	2	9	9	—	—	9	11	—
	P	5	10	5	—	5	8	7	—	—	4	14	2
General body tone	S	—	5	15	—	—	3	17	—	—	3	17	—
	T	1	7	12	—	—	10	10	—	—	5	15	—
	P	—	10	10	—	1	8	11	—	—	3	16	1
Rooting	S	2	12	6	—	—	10	8	2	3	8	9	—
	T	1	11	7	1	3	11	6	—	1	12	7	—
	P*	8	8	4	—	5	7	5	3	3	8	7	2
Sucking	S	2	2	16	—	—	4	15	1	2	7	11	—
	T	—	5	15	—	—	6	13	1	1	5	10	4
	P	3	6	10	1	1	4	10	5	3	4	13	—
Moro	S	—	6	12	2	—	5	14	1	—	6	13	1
	T	—	3	13	4	—	8	11	1	—	6	13	1
	P	—	7	12	1	—	7	11	2	—	6	13	1
Sound	S	8	9	3	—	5	7	7	1	4	10	5	1
	T†	10	7	3	—	9	11	—	—	4	9	7	1
	P	6	14	—	—	3	15	1	1	7	6	6	1
Placing	S	—	9	9	2	—	4	13	3	—	2	11	7
	T	—	9	9	2	—	5	14	1	1	5	13	1
	P§	1	15	4	—	—	8	11	1	—	9	11	—
Alertness	S	1	15	4	—	5	10	5	—	6	6	7	1
	T†	3	12	5	—	12	7	1	—	9	6	5	—
	P**	12	7	1	—	8	10	2	—	7	6	7	—

TABLE V. *Mean (SD) decremental counts in habituation to pinprick, Moro, light and sound at 1, 4 and 24 h in spontaneous vaginal delivery (S), thiopentone (T) and propofol (P) groups* ($n = 20$ *for each group*). **Significant difference from spontaneous delivery group:* *$P < 0.05$; **$P < 0.01$; ***$P < 0.02$

		Spontaneous delivery group	Thiopentone group	Propofol group
Pin-prick	1 h	6.7 (3.2)	6.6 (2.6)	6.2 (2.2)
	4 h	6.8 (2.3)	6.8 (2.4)	6.4 (3.1)
	24 h	8.3 (3.3)	6.4 (2.0)***	7.7 (2.7)
Moro Threshold	1 h	1.7 (1.1)	1.7 (0.6)	1.3 (0.5)
	4 h	1.9 (1.5)	2.1 (0.7)	1.8 (0.8)
	24 h	2.4 (1.2)	1.9 (0.6)	1.8 (0.8)
Extinguishment	1 h	8.1 (2.8)	7.1 (3.4)	5.3 (2.4)**
	4 h	7.6 (2.1)	6.4 (3.3)	7.5 (4.3)
	24 h	7.6 (2.9)	5.6 (2.6)*	7.7 (3.0)
Light	1 h	8.9 (6.0)	6.9 (1.8)	6.0 (2.9)*
	4 h	7.8 (3.9)	7.4 (4.9)	6.5 (3.7)
	24 h	8.8 (4.8)	6.5 (2.7)	6.3 (3.1)
Sound	1 h	2.9 (2.9)	2.4 (3.0)	2.6 (2.7)
	4 h	3.4 (2.5)	3.1 (3.5)	2.9 (2.0)
	24 h	3.8 (2.6)	3.0 (2.7)	2.7 (2.4)

of these neonates had a prolonged U–D interval (150 s).

The predominant initial state of the infant before examination was Scanlon's A1 at a 1 h in all the three groups; A1 in the propofol and control groups and A1–S2 in the thiopentone group at 4 h; S1 in the propofol group, A1–S2 in the thiopentone group and S1 in controls at 24 h. Irritability and continuous crying were noted in five neonates (25 %) of the propofol group during the 1-h examination. This irritability was not present at 4 h. The predominant state throughout the entire examination was the awake state in all neonates at 1, 4 and 24 h. The mean number of changes of state during examination (labile state) is shown in table III. Neonates in the propofol group showed a significant reduction in labile state at 24 h ($P < 0.02$ *v.* controls and $P < 0.01$ *v.* thiopentone group).

There were no significant differences between the groups in motor tone tests at 1, 4 and 24 h (table IV). Infants in the propofol group scored lower for pinprick at 1 h compared with infants in both the thiopentone group ($P < 0.002$) and the spontaneous vaginal delivery group ($P < 0.02$). This difference was no longer significant at 4 h. Infants in the propofol group scored lower also for placing reflex at 1 h compared with both control groups ($P < 0.05$), and in rooting reflex compared with the thiopentone group at 1 h ($P < 0.05$). These differences were not present at 4 and 24 h. Babies in the thiopentone group scored lower for sound than those in the spontaneous delivery group, at 4 h ($P < 0.05$). There was a significant depression of the state of alertness at 1 h in neonates whose mothers received propofol compared with the other two groups (table V). Compared with babies delivered spontaneously, infants whose mothers received thiopentone became tolerant to pinprick and to Moro significantly less quickly at 24 h, and infants in the propofol group required significantly fewer trials to modify the Moro reflex and light reaction at 1 h.

DISCUSSION

In this study, we attempted to reduce all prenatal or perinatal factors which might have negative effects on neurobehavioural responses [9, 10]. All mothers had an uncomplicated obstetric history and elective Caesarean delivery. The infants were comparable in all measured variables and they were examined in the same environmental conditions. Previous studies [11] have demonstrated that maternally administered thiopentone has a non-specific generalized depressant effect on the newborn. These data were not confirmed in the present study. Only a few neurobehavioural variables were affected briefly in the thiopentone group. This discrepancy in findings may result from different evaluation of Scanlon's scores. In the study of Hodgkinson and colleagues [11], the scores were classified as "high" or "low" and not on a four-point ordinal scale; the decremental responses were combined and not assessed separately, and the I–D and U–D intervals were not recorded. It is not clear if the drug–delivery interval influences exposure of the fetus to drug [12]. Nevertheless, in our study the I–D and U–D intervals were reasonably short and neonatal neurobehaviour was not greatly different from that of neonates delivered without general anaesthesia. The dose of propofol administered in this study was 2.8 mg/kg PBW—slightly greater than the usual recommended dose of 2.5 mg/kg PBW [13]. This dose was given according to the clinical judgement of the anaesthetist. It has been reported previously that a shorter mean induction time with a dose of 2.7–3 mg kg^{-1} did not increase side effects [14].

At birth, infants delivered from mothers who received propofol achieved significantly lower Apgar scores than controls, and 25% of them were hypotonic. This was no longer evident at 1 h. However, infants in the propofol group had a reduction in withdrawal reflex at 1 h compared with the two control groups, and a reduction in the placing reflex. This is a postural reflex integrated at various levels in the CNS from spinal cord to cerebral cortex and affected largely by extrapyramidal motor pathways [15]. Cortical depression produced by propofol would affect this reflex in the first 1 h of life. This depression could be responsible also for the irritability noted at the 1-h examintion in 25% of infants and for the significant reduction in lability at 24 h.

These neurobehavioural differences between the neonates in the thiopentone and propofol groups may be explained on the basis of pharmacokinetic differences [16]. Both thiopentone and propofol cross the placenta readily. Thiopentone has been reported to have a UV : MV ratio equal to 1 [12], and propofol a mean ratio of 0.7 [3]. In addition, the different metabolism of the two drugs may play a role in their neonatal effects. Pregnancy alters maternal clearance of thiopentone by alteration in hepatic drug-metabolizing enzymes and, less, by changes in liver blood flow [17]. Although there may be other factors to explain the lack of fetal depression [18, 19], rapid maternal redistribution has been considered the most likely cause [12]. There are no data on the pharmacokinetics of propofol in pregnancy, but studies on female patients confirm the hepatic metabolism of this drug and suggest also an extrahepatic component [16]. The neonatal clearance of propofol is unknown.

Our data suggest that thiopentone remains the drug of choice for induction of general anaesthesia for Caesarean section. Propofol may be used as an alternative, but not for high-risk pregnancy.

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DOSE–RESPONSE CURVES FOR SUXAMETHONIUM IN NEONATES, INFANTS AND CHILDREN

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SUMMARY

Single dose–response curves were determined for suxamethonium in neonates, infants and children during thiopentone–fentanyl–nitrous oxide anaesthesia. During onset of neuromuscular block, suxamethonium produced an increase in muscle tone which was greatest in neonates and infants. The dose–response curves for the three groups were parallel. The effective doses producing 90% depression of twitch height were significantly greater in neonates and infants compared with children (517 and 608 v. *352 μg kg⁻¹). These values were greater than those obtained in a comparable study in adults. In view of their higher ED values compared with adults and a marked individual variability in response to small doses of suxamethonium, we recommend an intubating dose of 3 mg kg⁻¹ for neonates and infants and 2 mg kg⁻¹ for children. These doses are 50–100% greater than those previously recommended for paediatric patients.*

Suxamethonium is used widely in paediatric anaesthesia to facilitate tracheal intubation for short surgical procedures. Despite reports that, on a weight basis, small infants require more suxamethonium than adults [1–5], and a recent suggestion that inadequate relaxation following suxamethonium may play a role in the production of jaw stiffness in children [6], there have been no definitive studies to establish single dose–response relationships. In the present study, the dose–response curves and the effective doses (ED) of suxamethonium producing 50, 90 and 95% depression of twitch height were determined in neonates, infants and children during thiopentone–fentanyl–nitrous oxide anaesthesia.

PATIENTS AND METHODS

Following approval by the District Ethics Committee, we studied 45 paediatric surgical patients comprising 15 neonates (median age 12 days, range 1–25), 15 infants (median age 5.2 months, range 1.3–10.9), and 15 children (median age 4.2 yr, range 1.4–7.3). All were ASA class I and none was receiving any drug known to interfere with neuromuscular transmission.

No premedication was given. In all subjects anaesthesia was induced with thiopentone 6–8 mg kg^{-1} and fentanyl 2 μg kg^{-1}. Anaesthesia was maintained with 70% nitrous oxide in oxygen, supplemented with thiopentone as required. Intubation of the trachea was performed during anaesthesia, without the aid of neuromuscular blockade. Ventilation was controlled using the paediatric attachment of the Blease ventilator. End-tidal carbon dioxide partial pressure was monitored using a Datex capnograph, and maintained in the range 5.0–5.5 kPa. Rectal temperature was maintained at 36.5–37.5 °C.

Neuromuscular transmission was monitored using the method of Ali, Utting and Gray [7]. The ulnar nerve was stimulated supramaximally at the wrist via small silver electrodes applied to the skin with adhesive electrode paste. Train-of-four stimulation with square pulses of 0.2 ms duration at a frequency of 2 Hz was repeated every 10 s using a Grass S48 stimulator and SIU5 isolation unit. The hand and forearm were immobilized in a splint and the force of thumb adduction was measured using a strain gauge transducer (Grass FT03) and recorded on a pen-and-ink recorder (Grass polygraph).

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Following a period of 10–12 min to allow stabilization of the train-of-four responses, suxamethonium was administered by rapid (5-s) i.v. injection. In order to construct dose–response curves, the 15 patients in each age group were allocated randomly to three sub-groups of five, to receive suxamethonium 200, 300 or 400 $\mu g\ kg^{-1}$. These doses were chosen following a preliminary trial to determine the approximate position of the dose–response curves. All the suxamethonium used in the study was from the same batch and was kept refrigerated before use.

Before regression analysis, doses were transformed into logarithmic data and depression of twitch height was transformed into probit values. These transformations convert the sigmoid dose–response relationship for neuromuscular block into a straight line [8, 9]. Log–probit regression lines were calculated using the iterative least squares method of Finney [10]; calculations were performed on a PRIME 9955 computer using a Rothamstead statistical package, GLIM 3.77. The fitted lines were tested for parallelism and identity using the *F* ratio test. Statistical differences between pairs of intercepts and group ED values were determined using a Student's *t* test based on the covariance matrix output from GLIM 3.77. Bonferroni's correction for multiple comparisons was applied to the resulting probabilities, and the null hypothesis was rejected when $P < 0.05$.

RESULTS

In all patients, neuromuscular block induced by suxamethonium was preceded by a detectable elevation of the baseline, signifying increased muscle tone (fig. 1). In 10 neonates, four infants and one child, this increase was in the range 6–25% of control twitch height. Applying Fisher's exact probability test to these data, marked increases in muscle tone occurred more frequently in neonates than in infants ($P < 0.05$), and more frequently in neonates and infants combined than in older children ($P < 0.01$). Following recovery from suxamethonium, an increase in height of the train-of-four response was observed in all patients in whom recordings were made ($n = 34$) (fig. 1). The size of the overshoot ranged from 3% to 22%, and there was no apparent difference in either the magnitude or incidence of overshoot between the groups.

In two patients, one neonate (fig. 1B) and one child, depression of twitch height was much less than anticipated (1% and 3%, respectively), and we initially considered excluding these data from the regression analysis. However, as no arithmetical error was discovered, and examination of the raw data showed elevation of the baseline and overshoot consistent with suxamethonium having been given, it was decided that these observations should be retained.

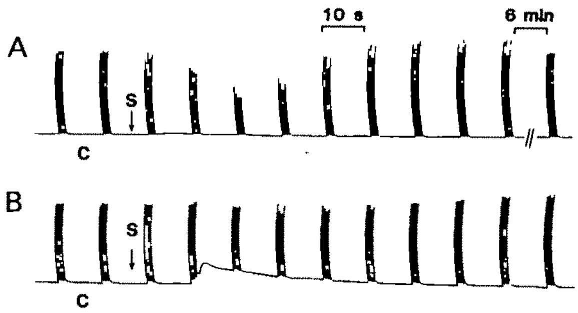

FIG. 1. Train-of-four recordings obtained from an infant (A) and a neonate (B). Following administration of suxamethonium 0.3 $mg\ kg^{-1}$ (S), recording A shows a slight elevation of the baseline before depression of T1 to approximately 50% of control. Recovery from maximum depression to control twitch height is rapid (25 s) and this is followed by a period of increased twitch height (17%) lasting 5–6 min. Compared with recording A, recording B shows much greater elevation of the baseline (25%), but depression of twitch height is far less (1%). Following recovery from suxamethonium, a similar degree of overshoot of the twitch response is seen in recording B as in recording A.

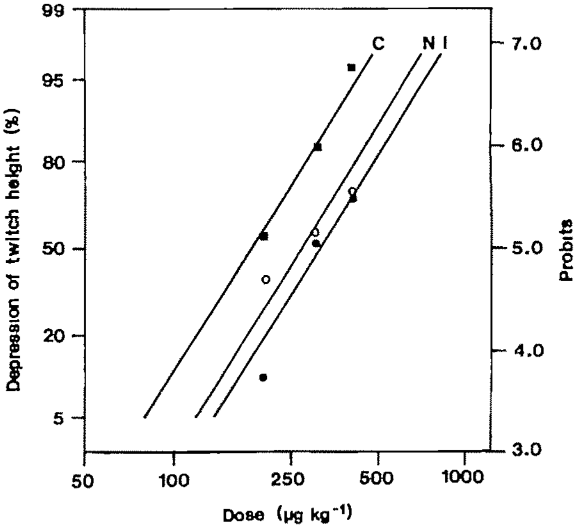

FIG 2. Log dose–probit response regression lines for neonates (N), infants (I) and children (C). Points along the lines represent mean responses from sub-groups of five patients

Figure 2 illustrates the fit of the regression lines

TABLE I. *Calculated values of ED_{50}, ED_{90} and ED_{95} (SEM). The initials N = neonates, I = infants, C = children indicate significant differences between the groups concerned*

	Neonates	Infants	Children
ED_{50} ($\mu g\ kg^{-1}$)	270 (19)	317 (23)	184 (18)
ED_{90} ($\mu g\ kg^{-1}$)	517 (60)	608 (81)	352 (32)
ED_{95} ($\mu g\ kg^{-1}$)	620 (86)	729 (115)	423 (46)
$P < 0.01$	C		N
$P < 0.001$		C	I

with the mean dose–response data for the three groups of patients. The weighted regression coefficient (common slope) was 1.97 probits $\log^{-1}$. Allowing the slopes to differ did not improve the fit of the lines as measured by the F ratio test, so these were not significantly different. However, the test showed that the positions of the lines (intercepts) were not identical ($P < 0.001$). When individual group values were compared, the intercepts and the ED values neonates and infants were found to be significantly different from those found in children ($P < 0.01$, $P < 0.001$, respectively) (table I).

DISCUSSION

Our data indicate that, when dose is based on body weight, neonates and infants are resistant to the neuromuscular blocking effects of suxamethonium compared with older children, confirming earlier reports in paediatric patients [1–5].

A comparable study in adults gave an ED_{90} for suxamethonium of 290 $\mu g\ kg^{-1}$ [11]. Thus on the basis of ED_{90} values, neonates and infants require approximately twice as much suxamethonium as adults, while children require 20% more (table II). As adults usually receive suxamethonium 1–1.5 mg kg^{-1} for intubation, neonates and infants should receive 2–3 mg kg^{-1} and children 1–2 mg kg^{-1}. In view of the marked variability in neuromuscular block produced by small doses of suxamethonium in this and earlier studies [12–14], it would seem advisable to select doses at the upper end of these ranges. Accordingly, we recommend a dose of at least 3 mg kg^{-1} for infants and 2 mg kg^{-1} for children. These doses are 50–100% greater than those recommended previously for paediatric patients [15].

TABLE II. *Ratio of paediatric to adult ED_{90} values; calculated equipotent doses of suxamethonium*

	Suxamethonium ED_{90} (mg kg^{-1})	ED_{90} ratio	Calculated equipotent doses (mg kg^{-1})
Neonates	0.517	1.8	1.8–2.7
Infants	0.608	2.1	2.1–3.2
Children	0.352	1.2	1.2–1.8
Adults [11]	0.290	1.0	1.0–1.5

TABLE III. *ED_{90} values for patient groups. Conversion from mg kg^{-1} to mg m^{-2} compensates for larger ECF volume in younger patients*

	ED_{90}	
	mg kg^{-1}	mg m^{-2}
Neonates	0.517	8.24
Infants	0.608	12.04
Children	0.352	8.45
Adults [11]	0.290	11.94

Resistance to suxamethonium in younger patients is thought to result from its initial rapid distribution into a large volume of extracellular fluid (ECF) [4]: ECF constitutes 45% of the body weight in neonates, 30% at age 2 months, 20% at age 6 yr and 16% in adults [16]. The observation that giving suxamethonium on an mg m^{-2} basis abolishes the differences in dose requirement between age groups supports this suggestion, as ECF volume and body surface area bear a nearly constant relationship throughout life [3, 17]. Table III shows the effect of converting the ED_{90} values of our patients from mg kg^{-1} to mg m^{-2}, using the formula of Dubois [18]. The differences between the groups are considerably reduced, and paediatric patients no longer appear resistant to suxamethonium when compared with adults.

Increases in muscle tone during onset of neuromuscular block with suxamethonium, and overshoot following recovery (fig. 1), have been observed previously in human and animal studies [19–21]. Using simultaneous twitch and electromyographic (EMG) recordings to monitor suxamethonium-induced neuromuscular block, Donati and Bevan have shown that twitch augmentation during onset, but not during recovery, was accompanied by a change in the EMG [22]. They suggested that the increased twitch during onset may result from repetitive firing of muscle fibres, while that during recovery may result from improved muscle contractility.

The increase in muscle tone during onset of neuromuscular block with suxamethonium has been implicated as a cause of masseter spasm in children [23]. However, as this increase in tone apparently occurs in all children following suxamethonium, and the reported incidence of masseter spasm is only 1 in 100 [24,25], some additional condition or mechanism may be implicated. One possibility is that the increase in muscle tone may be greater during light anaesthesia. This could explain why the neonates and infants in our study had greater increases compared with older children, as it is likely that these patients received less thiopentone before injection of suxamethonium. Another possibility, suggested by the higher dose requirements in paediatric patients compared with adults (table II), is that children may frequently be given too little suxamethonium. In these circumstances, poor intubating conditions could be the result of inadequate neuromuscular block alone, or in combination with the often marked increases in muscle tone we observed with small doses of suxamethonium.

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USE OF ATRACURIUM OR VECURONIUM TO PROLONG THE ACTION OF TUBOCURARINE

C. M. MIDDLETON, B. J. POLLARD, T. E. J. HEALY AND B. KAY

SUMMARY

Forty patients received tubocurarine in a dose greater than ED_{90}. When neuromuscular function had recovered to amplitude of the first contraction of the train-of-four equals 10% of control, a small increment of atracurium or vecuronium was administered, repeating the same increment at each subsequent recovery to 10%. The intensity and duration of the neuromuscular block following the first increment was always greater than that of subsequent increments. The duration and intensity of the block was progressively reduced with subsequent increments until the responses to further increments were unchanged. These final means at steady state were: group 1 (atracurium 1.1 mg) 6.4 (0.3) min; group 2 (atracurium 2.0 mg) 8.2 (0.9) min; group 3 (vecuronium 0.25 mg) 5.8 (0.4) min; group 4 (vecuronium 0.5 mg) 13.2 (0.4) min.

The waning effect of neuromuscular blocking agents towards the end of surgery often necessitates the addition of a further increment of blocker. When a longer acting agent (e.g. tubocurarine or pancuronium) is used, this additional increment may delay recovery [1]. Atracurium and vecuronium, the two intermediate acting agents, may be used for longer surgical procedures, although repeated bolus administration or continous infusion is required [2, 3].

It would seem logical to use a longer acting agent to produce initial neuromuscular block and to use atracurium or vecuronium if extension of the block is needed. This technique is satisfactory with pancuronium and vecuronium [4], but no data are available for the other agents. We have therefore examined the effect of atracurium and vecuronium when given to supplement an existing neuromuscular block produced by tubocurarine.

PATIENTS AND METHODS

The study was approved by the hospital Ethics Committee and informed consent obtained from 40 ASA I or II patients scheduled to undergo major gynaecological surgery. Those patients with a history of renal, hepatic or neuromuscular disease and those taking medication known to interfere with neuromuscular function were excluded. All patients were premedicated with lorazepam 2–3 mg given by mouth 90–120 min before surgery. When the patient arrived in the anaesthetic room, surface electrodes were applied to the hand and wrist. The compound evoked electromyogram was recorded over the adductor pollicis muscle after stimulation of the ulnar nerve (Datex Relaxograph). Anaesthesia was induced using thiopentone 4 mg kg^{-1} and fentanyl 2 μg kg^{-1} and ventilation controlled with 67% nitrous oxide in oxygen to maintain normocapnia.

Neuromuscular function was monitored continuously throughout anaesthesia using trains of four supramaximal stimuli every 20 s. After baseline measurements of neuromuscular function, an initial dose of tubocurarine 0.35 mg kg^{-1} was given. Additional increments of tubocurarine 0.05 mg kg^{-1} were given in close succession, if needed, until neuromuscular block exceeded 90%. The trachea was intubated and controlled ventilation, maintaining normocapnia, continued using 67% nitrous oxide in oxygen. Further doses of fentanyl to a maximum of 10 μg kg^{-1} were

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administered as required during the procedure, together with droperidol to a maximum of 10 mg.

Continuous ECG and pulse wave were monitored during operation. Arterial pressure was measured automatically (Dinamap). When neuromuscular function had recovered such that the amplitude of the first contraction of the train-of-four (T1) had reached 10% of control, an increment of atracurium or vecuronium was given. At each subsequent T1 recovery to 10% the same dose of the same drug was administered.

Patients were allocated randomly to one of four groups: groups 1 and 2 received increments of atracurium 1.1 mg or 2 mg, respectively; groups 3 and 4 received increments of vecuronium 0.25 mg or 0.5 mg, respectively. Atracurium 1.1 mg and vecuronium 0.25 mg increments were chosen because they are equipotent at the 90% level of neuromuscular block [5]. Vecuronium 0.5 mg was chosen because it was twice the dose given to group 3, and for comparison with previous studies. Atracurium 2 mg was chosen as a convenient dilution of the agent which approximated to twice the dose used in group 1. Following each increment of atracurium or vecuronium, maximum T1 depression and the time to achieve maximum neuromuscular block were recorded. The duration of effect of each increment was also recorded, as measured by the return of T1 to 10%. At the termination of surgery, all patients received i.v. glycopyrrolate 0.01 $\mu g\ kg^{-1}$ and neostigmine 0.05 $\mu g\ kg^{-1}$ to accelerate recovery of neuromuscular function.

A supply of atracurium ampoules which had been maintained refrigerated from manufacture was used. Both atracurium and vecuronium were diluted freshly with 5% dextrose for each subject. All drugs were administered into a fast-running i.v. infusion.

Statisical analysis

The age, weight, dose of tubocurarine and duration of those doses were compared between groups, using one-way analysis of variance. These four variables were considered as potential co-variates in subsequent analyses. The remaining data were found to conform to a log-normal distribution, and this transformation was used for subsequent data analysis. Analysis of variance was performed to determine the presence of any significant difference between the groups and between increments within the groups. Tukey's range test was used to identify the source of those significant differences.

RESULTS

The mean ages and weights of the patients in the four groups did not differ significantly (table I). The dose of tubocurarine required to achieve a greater than 90% neuromuscular block was between 0.35 $mg\ kg^{-1}$ and 0.70 $mg\ kg^{-1}$. These

TABLE I. *Details of patients (mean (SEM))*

	Age (yr)	Weight (kg)
Group 1 (Atracurium 1.1 mg)	43.1 (2 56)	65.0 (3.99)
Group 2 (Atracurium 2 mg)	44.6 (4.43)	66.9 (3.39)
Group 3 (Vecuronium 0.25 mg)	43.7 (4.52)	63.9 (2.95)
Group 4 (Vecuronium 0.5 mg)	42.0 (1.05)	59.2 (2.33)

TABLE II. *Total dose, duration of action until return to T1 of 10% and maximum block resulting from the intubating dose of tubocurarine (mean (SEM))*

	Tubocurarine dose ($mg\ kg^{-1}$)	Time to return to T1 = 10% (min)	Mean maximum block
Group 1 (Atracurium 1.1 mg)	0.42 (0.02)	22.9 (2.9)	93.1 (0.3)
Group 2 (Atracurium 2 mg)	0.52 (0.04)	25.9 (1.9)	92.2 (0.7)
Group 3 (Vecuronium 0.25 mg)	0.44 (0.03)	24 9 (3.2)	94.6 (0.5)
Group 4 (Vecuronium 0.5 mg)	0.50 (0.04)	28.3 (2.0)	98.1 (0.6)

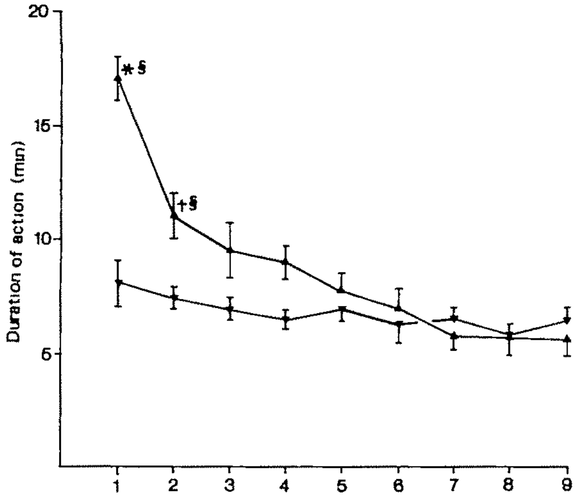

FIG. 1. Duration of action of atracurium 1.1 mg (▼) (group 1) or vecuronium 0.25 mg (▲) (group 2) from administration until the return of T1 of the train-of-four to 10%. Significant differences ($P < 0.05$) within group: *greater than all other increments, †greater than increments 5–9. §Significantly greater ($P < 0.05$) than corresponding increment of atracurium.

mean doses are displayed for each group in table II, together with the mean duration of action and mean maximum block achieved. None of these observations differed significantly between the groups.

The duration of action of the first increment of each drug was the longest, decreasing with successive increments until the duration of effect of each increment became constant. This steady state was reached sooner in the atracurium groups (approximately increment 3) than in the vecuronium groups (approximately increments 6 or 7) (figs 1, 2). The overall mean of the values for increments 7–10 was taken as representative of the final steady state duration of action for each group. These were (mean (SEM)): group 1 (atracurium 1.1 mg) 6.39 (0.30) min; group 2 (atracurium 2 mg) 8.19 (0.94) min; group 3 (vecu-

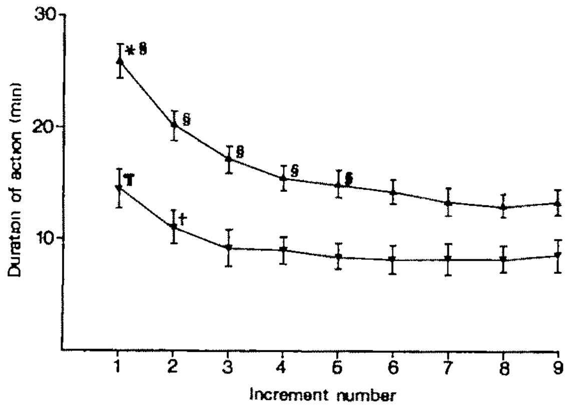

FIG. 2. Duration of action of atracurium 2 mg (▼) (group 3) or vecuronium 0.5 mg (▲) (group 4) from administration until the return of T1 of the train-of-four to 10%. Significant differences ($P < 0.05$) within group: *greater than all other increments: ¶greater than increments 3–9; †greater than increments 5–9. §Significantly greater ($P < 0.05$) than corresponding increment of atracurium.

TABLE III. *Geometric mean (adjusted for patients' weight, tubocurarine dose, and duration of tubocurarine dose) maximum T1 depression and arithmetic mean (SEM) times to maximum T1 depression (data from increments 5–10 combined). All statistical significances are shown when less than 5% (P < 0.05) and the actual probability level, which may be greater than 5%, is not reported. Significant differences in corresponding increments between groups: *Less than all other groups; †greater than all other groups; ‡less than groups 3 and 4; §less than group 4; ¶greater than groups 1 and 3. Significant differences within groups: **Increments from 5th increment onwards less than the first increment for that group; †† less than the first or second in this group*

	Mean maximum depression of T1 (%)					Mean time to maximum depression of T1 (min)				
Increment:	1	2	3	4	5+	1	2	3	4	5+
Group 1 (Atracurium 1.1 mg)	3.13*	2.74*	2.60*	2.71	2.96	2.33‡ (0.43)	2.59‡ (0.35)	2.05‡ (0.14)	2.48§ (0.22)	1.95 (0.22)
Group 2 (Atracurium 2 mg)	4.98	4.81	4.43	4.11¶	3.55**	2.78‡ (0.67)	3.33 (0.38)	1.92‡ (0.29)	2.15§ (0.28)	2.32 (0.24)
Group 3 (Vecuronium 0.25 mg)	4.56	4.44	3.78	2.94††	2.35**	4.92 (0.56)	3.83 0.41)	3.79 (0.32)	3.47 (0.36)	2.40** (0.14)
Group 4 (Vecuronium 0.5 mg)	7.68†	7.94†	7.46†	7.80†	6.84†	4.34 (0.81)	4.36 (0.64)	4.42 (0.81)	3.72 (0.57)	4.14† (0.41)

TABLE IV. *Mean rates of use of atracurium and vecuronium*

	Rate of use	
	($mg\ h^{-1}$)	($mg\ kg^{-1}\ h^{-1}$)
Group 1 (Atracurium 1.1 mg)	10.2	0.16
Group 2 (Atracurium 2.0 mg)	14.5	0 22
Group 3 (Vecuronium 0.25 mg)	2.6	0.04
Group 4 (Vecuronium 0.5 mg)	3.1	0.05

ronium 0.25 mg) 5.82 (0.41) min; group 4 (vecuronium 0.5 mg) 13.25 (0.40) min.

The mean maximum neuromuscular block resulting from each increment, together with the times to achieve this maximum for all groups are shown in table III. Analysis of the maximum depression showed that there were significant effects of three of the covariates on this variable. The maximum T1 depression increased with the weight of the patient and with the dose of tubocurarine and decreased with the duration of the tubocurarine dose. The means as presented in table III are therefore adjusted for these three covariates. In every case, the first increment had the greatest effect, reducing successively with the following increments. In most instances the maximum depression with vecuronium was greater than with the corresponding atracurium increments (groups 1 and 3 compared; groups 2 and 4 compared). The times to reach maximum T1 depression in the atracurium groups were significantly less than the vecuronium groups for most increments. There was little change in the times to maximum T1 depression within the groups.

Using the duration of action of each increment in each group at steady state and the mean weight of the patients in the four groups, the average rate of use of each agent was calculated (table IV).

DISCUSSION

The overall mean intubating dose of tubocurarine, 0.45 mg kg^{-1} (range 0.35–0.7), resulted in a mean maximum neuromuscular block of 97% (range 93–100). This agrees well with data from previous studies in which the ED_{95} for tubocurarine has been reported to be between 0.34 and 0.56 mg kg^{-1} (mean of 0.48 mg kg^{-1}) [6].

Following the intubating dose of tubocurarine, the great majority of neuromuscular receptors are occupied by tubocurarine molecules and at 90% neuromuscular block (10% recovery) they are still occupied predominantly by tubocurarine molecules. The addition of a small increment of either atracurium or vecuronium at that point would be expected to result in a further increase in receptor occupancy. This increase in receptor occupancy by antagonist molecules is likely to lead to an increase in neuromuscular block. The identical increments of atracurium or vecuronium add each time a similar amount to the increasing concentration of the second agent in plasma and at the receptor site. Assuming that both agents possess first order pharmacokinetics, this change in concentration is greatest with the first increment as the concentration increases from zero and reduces with successive increments. The effects of earlier increments should therefore last longer than later increments. It is possible that the decrease in duration of effect from the first increment is at least partly a result of this principle.

The action of the tubocurarine continues to wane with time as molecules leave the region of the neuromuscular junction. The rate of loss of tubocurarine molecules from the region of the neuromuscular junction also changes with time and in an exponential fashion. Initially, recovery is likely to result from removal of tubocurarine molecules. With time, the recovery from each increment should be less because of clearance of tubocurarine and more because of clearance of the second agent. Ultimately, the situation might present where molecules of both agents are leaving at approximately the same rate as molecules of the shorter acting agent are arriving and, under these circumstances, identical increments should have an identical action. At this steady state, a significant proportion of receptors must still be occupied by tubocurarine (or some other residual effect of tubocurarine persist), otherwise there is no reason why such a small dose of atracurium or vecuronium should produce a neuromuscular block in excess of 90%.

In a system where there is competitive interaction at a single receptor site the observed effect, as a proportion of the maximum possible effect, is proportional to receptor occupancy. Identical amounts of an antagonist add identical numbers of molecules to the biophase and thus should produce an identical change from a given point in the system. In the present study, successive increments did not produce identical effects. Furthermore, the extension of neuromuscular block and the intensity of effect were greater with vecuronium than with an equipotent dose of atracurium. Such an observation cannot be explained fully by simple interaction at one receptor site or by the pharmacokinetic effects discussed previously. In addition, any action of the second agent on the receptor affinity of the first is not known. Evidence exists to suggest that the neuromuscular junction is not a simple receptor system and it is likely, therefore, that the three agents, tubocurarine, atracurium and vecuronium, are all acting in slightly different ways. Previous reports have suggested that the combination of tubocurarine with some other neuromuscular blocking agents may not lead to simple addition of action [7, 8].

Significant effects were observed of three covariates on the maximum depressions resulting from each increment. It is difficult to be certain of the mechanisms involved. The maximum T1 depression increased with increasing weight of the patients. Although no measures were taken of height or body fat content (all patients were female) larger patients should have a greater distribution volume and therefore a small fixed increment would be expected to have less, not greater effect. The maximum T1 depression increased also with the dose of tubocurarine and decreased with time before return to 10%. Following a larger initial dose of tubocararine (on an mg kg^{-1} basis) or where less time has elapsed since the intubating dose, the quantity of tubocurarine in the active biophase when the first increment was given would be expected to be greater. This does, however, discount binding to extrajunctional receptors, elimination and other distribution effects, all of which play an important and unquantifiable role.

The rates of use of both atracurium and vecuronium have been calculated at steady state. If one of these two is used as sole neuromuscular blocking agent, the rate of use for the maintenance of 90–95% neuromuscular block would be expected to be approximately 0.366–0.432 mg kg^{-1} h^{-1} for atracurium and 0.055–0.102 mg kg^{-1} h^{-1} for vecuronium [6]. It is clear, therefore, that the presence of a partial tubocurarine block would reduce considerably the rate of consumption of both atracurium and vecuronium.

These results may be viewed in two ways. On the one hand, the action of a small dose of atracurium or vecuronium is increased in the presence of a tubocurarine-induced neuromuscular block. On the other, a tubocurarine-induced neuromuscular block may be usefully extended by very small doses of either atracurium or vecuronium. Whichever view is taken, this technique is attractive and has proved convenient in regular clinical use.

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DOXAPRAM AND THE NEUROMUSCULAR JUNCTION†

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The respiratory stimulant doxapram has been in clinical use for many years. It stimulates respiration by an action secondary to an increase in the sensitivity of both central and peripheral chemoreceptors [1], thereby increasing minute ventilation [2] and accelerating recovery from volatile anaesthetic agents [3]. There is no effect on analgesia [2]. This study was designed to see if doxapram has any effect on the neuromuscular junction.

METHODS

Male Sprague–Dawley rats (weights 250–400 g) were killed and both hemidiaphragms removed with accompanying phrenic nerves. Each hemidiaphragm was attached to a Perspex carrier assembly, and placed in an organ bath of 70 ml capacity filled with Krebs–Henseleit solution aerated with 5% carbon dioxide in oxygen. The composition of the solution was: Na^+ 143, Cl^- 129, K^+ 5.9, Ca^{2+} 3.3, Mg^{2+} 1.2, HCO_3^- 25, SO_4^{2-} 1.2, $H_2PO_4^-$ 1.2, glucose 11.1 mmol $litre^{-1}$.

Temperature was maintained at 36.5–37.5 °C and the muscles stretched lightly to a resting basal tension of 4 g and kept constant. Each preparation was stimulated indirectly via its phrenic nerve using square wave pulses of 0.2 ms duration at voltages greater than those producing a maximal response. The overall maximum rate of stimulation was 0.1 Hz and the resulting single muscular contractions were recorded isometrically and displayed on a Grass 79C Multichannel Polygraph. Some preparations were prepared for both direct and indirect stimulation. Direct stimulation was of 2 ms duration at 0.08 Hz and a voltage greater than that which produced a maximal response. At the end of the experiment, tubocurarine was added to the bathing solution to produce 100% inhibition of indirect stimulation.

SUMMARY

We have studied the action of doxapram on neuromuscular transmission in the rat phrenic nerve–diaphragm preparation. Doxapram augmented neuromuscular transmission in a dose-related manner when a threshold concentration of 5×10^{-5} mol $litre^{-1}$ had been exceeded. The activity of the acetylcholinesterase in rat diaphragm has been examined also in the presence of doxapram. No inhibitory effect was seen in the concentration range which augmented neuromuscular transmission, thus excluding cholinesterase inhibition as the underlying mechanism. In contrast, in the presence of partial neuromuscular block, a dose-related depression of neuromuscular transmission with doxapram was revealed. This was greatest when the neuromuscular blocking agents possessed significant presynaptic activity (β-bungarotoxin and tubocurarine). In this situation any facilitatory action of doxapram was severely reduced or abolished. In contrast, the facilitatory effects of doxapram were apparent in the presence of partial block produced by agents with less or no presynaptic activity (pancuronium and α-bungarotoxin). This study suggests that doxapram has a presynaptic facilitatory action at the neuromuscular junction. In the presence of partial neuromuscular block, an inhibitory action is revealed which may be post-junctional. The concentrations of doxapram at which these effects appear are approximately five times greater than those reached in plasma after a standard clinical dose.

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If the response to direct muscle stimulation also decreased, indicating a significant indirect component to the measured response, the results were discarded.

Doxapram alone

The preparations were used in pairs from the same rat, one receiving doxapram, the other serving as an exact time-matched control receiving equivalent volumes of distilled water. Doxapram was administered to the bath in a small volume, to achieve the following concentrations in the bath: 5×10^{-5} mol litre^{-1}, 1×10^{-4} mol litre^{-1}, 2.5×10^{-4} mol litre^{-1} and 5×10^{-4} mol litre^{-1}. Twenty minutes (or longer if necessary) was allowed for a steady state response to be achieved, after which doxapram was removed, using several changes of bathing solution. A series of different concentrations of doxapram was administered randomly to each preparation. The percent change in contraction at steady state was recorded and corrected for any change in the control preparation.

Doxapram in the presence of neuromuscular blocking agents

Blocking agents were selected which represented a range of sites of action, from mostly presynaptic (e.g. β-bungarotoxin [4]) through tubocurarine and pancuronium, to selective postsynaptic activity (e.g. α-bungarotoxin [5]). Concentrations of the agents were chosen to produce 0–30% inhibition of indirectly evoked contractions. After equilibration with the neuromuscular blocking agents (usually 30 min), the experiments described above for doxapram alone were repeated. The results obtained were compared with time-matched control preparations which had received the neuromuscular blocking agent but no doxapram.

Doxapram and cholinesterase

In this section, the action of doxapram on the cholinesterase from rat diaphragm was determined using the method of Ellman [6]. Acetylthiocholine, when hydrolysed to thiocholine by the cholinesterase in rat diaphragm homogenates, liberates thiocholine which combines with 5,5-dithiobis-(2-nitrobenzoic acid) to form a yellow-coloured ion, 5-thio-2-nitrobenzoate. This colour change can be measured spectrophotometrically at a wavelength of 412 nm and provides a measure of the percent cholinesterase inhibition.

Drugs

α- and β-bungarotoxins (Sigma Chemical Company) were prepared freshly in sodium phosphate buffer 0.1 mol litre^{-1} (pH 7.5). Tubocurarine chloride (Calmic) and pancuronium bromide (Organon-Teknika) were used as the commercially available solutions. Doxapram hydrochloride was used either as the commercially available solution or prepared freshly in aqueous solution from the pure substance supplied by A. H. Robins Co. Ltd.

Unless otherwise stated all results are expressed as mean (SEM).

RESULTS

Doxapram alone

A dose-dependent increase in the amplitude of contraction was seen in the presence of concentrations of doxapram in excess of 5×10^{-5} mol litre^{-1} and was confined to those contractions elicited by nerve stimulation (fig. 1). Doxapram was removed readily by the wash cycle used and repeated administration of the same concentration gave constant responses. In two preparations, concentrations of doxapram 1×10^{-4} mol litre^{-1} and 2.5×10^{-4} mol litre^{-1} were left in contact with the preparation for continuous periods of 1 h.

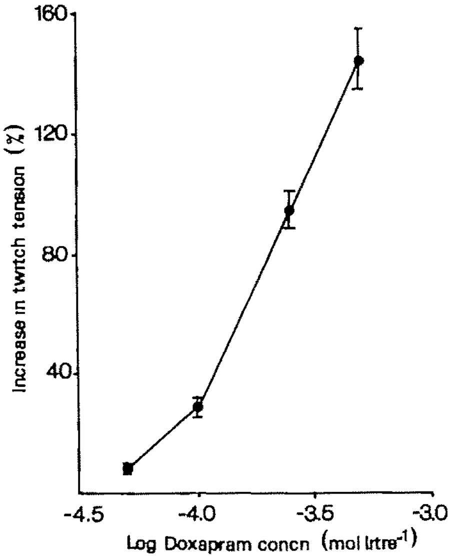

FIG. 1. Log concentration–effect relationship for the increase in twitch tension to doxapram alone ($n = 6$).

TABLE I. *Inhibitory action of doxapram on evoked twitch tension in the presence of partial neuromuscular block (mean % change (SEM)). Inhibition produced by the neuromuscular blocking agents is shown, followed by the results of the addition of doxapram (expressed as change from the immediately predoxapram twitch tension)*

	Initial block	Doxapram (mol litre^{-1})		
		1×10^{-4}	2.5×10^{-4}	5×10^{-4}
Tubocurarine (mol litre^{-1})				
2.5×10^{-7}	−3.9 (1.6)	−7.9 (10.0)	−42.4 (8.3)	−100
5×10^{-7}	−34.1 (5.4)	−21.9 (9.4)	−54.8 (10.3)	−100
Pancuronium (mol litre^{-1})				
5×10^{-7}	−2.2 (0.9)	No decrease	No decrease	−31.3 (22.7)
1×10^{-6}	−13.2 (1.6)	No decrease		−100
2×10^{-6}	−18.4 (2.6)	No decrease	−47.8 (16.2)	−100
α-Bungarotoxin				
0.1 μg ml^{-1}	−16.3 (2.4)	No decrease	No decrease	−11.2 (10.0)

Potentiation was sustained throughout this time with normal recovery on removal of doxapram. Both commercial solutions of doxapram and solutions prepared from the pure substance produced identical results.

Doxapram in the presence of neuromuscular blocking agents

The addition of tubocurarine 5×10^{-7} mol litre^{-1} produced a mean depression of indirectly evoked contraction of 34.1%. In the presence of this concentration of tubocurarine, no increase in height of contraction was seen when doxapram was introduced. Instead, a dose-dependent depression of twitch height was seen, beginning at concentrations of doxapram greater than 5×10^{-5} mol litre^{-1} and increasing to 100% depression with concentrations in excess of 5×10^{-4} mol litre^{-1} (table I).

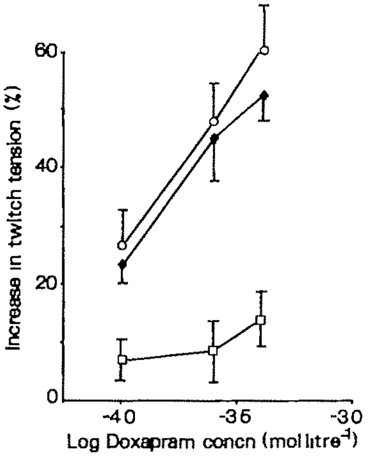

FIG. 2. Log concentration–effect relationships for the increase in twitch tension to doxapram in the presence of tubocurarine 2.5×10^{-7} mol litre^{-1} (□), pancuronium 5×10^{-7} mol litre^{-1} (○) and α-bungarotoxin 0.1 μg ml^{-1} (◆) ($n = 8$).

In the presence of tubocurarine 2.5×10^{-7} mol litre^{-1}, which depressed the indirectly evoked contraction of the diaphragm by only 3.9 (1.4)%, doxapram produced initially a small increase in tension (fig. 2), followed by a decrease similar to that described with the higher concentration (table I). In contrast, in the presence of pancuronium 5×10^{-7} mol litre^{-1}, which depressed indirectly evoked contractions by a similar amount (2.2 (0.9%)), doxapram elicited a larger increase in tension (fig. 2). This was followed by a secondary decrease in tension only with the highest concentration of doxapram. Increasing the concentration of pancuronium progressively reduced the ability of doxapram to increase the contraction tension (fig. 3) and the subsequent depression produced by doxapram was enhanced (table I).

In the presence of α-bungarotoxin 0.1 μg ml^{-1}, the action of doxapram resembled that obtained with the smallest concentration of pancuronium, except that no significant secondary inhibition of contraction was obtained with even the highest concentration of doxapram (fig. 2, table I). However, this concentration of α-bungarotoxin produced an inhibition of twitch tension comparable to that associated with the highest concentration of pancuronium.

β-Bungarotoxin was difficult to use. The block

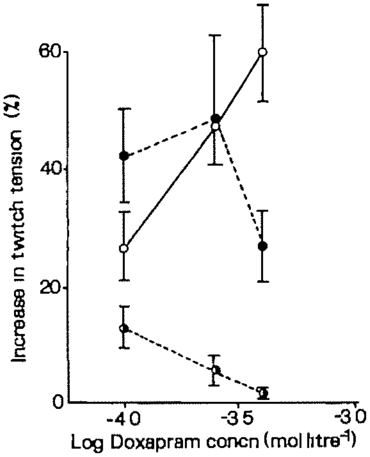

FIG. 3. Log concentration–effect relationships for the increase in twitch tension to doxapram in the presence of pancuronium 5×10^{-7} mol litre^{-1} (○), 1×10^{-6} mol litre^{-1} (●), and 2×10^{-6} mol litre^{-1} (◑) ($n = 6$).

of neurotransmission was slow to develop and increased progressively during the day, despite repeated washing with fresh Krebs–Henseleit solution. Thus it was not possible to assess the action of doxapram on partial block in equilibrium conditions.

The order of addition of doxapram concentrations was randomized from preparation to preparation, and when a measurable block of transmission had occurred with β-bungarotoxin 0.25 µg ml^{-1} no increase in twitch tension was seen with any concentration of doxapram. In contrast, an increase in the rate of progressive block was observed.

Doxapram and cholinesterase

In concentrations of 5×10^{-4} mol litre^{-1} and less, doxapram had no significant effect on the acetylcholinesterase of the rat diaphragm. When this concentration had been exceeded, however, inhibition occurred which became greater as the concentration of doxapram increased (table II). In the concentration range of doxapram that produced potentiation of neuromuscular transmission, doxapram did not inhibit acetylcholinesterase.

TABLE II. *Effect of doxapram on acetylcholinesterase activity (mean (SEM)) of rat diaphragm* ($n = 3$)

Doxapram concentration ($\times 10^{-4}$ mol litre^{-1})	Inhibition of cholinesterase (%)
0.625	5.89 (1.44)
1.25	9.14 (0.68)
2.5	3.26 (2.36)
5	7.31 (2.50)
10	16.03 (0.90)
20	23.11 (1.69)

DISCUSSION

Two differing actions of doxapram have been demonstrated on the rat phrenic nerve–diaphragm preparation.

When administered alone, doxapram augmented muscle contractions. The resulting potentiation was confined to contractions elicited by nerve stimulation, which implies an action either on the nerve or at the neuromuscular junction. The minimum concentration required to elicit this response was 5×10^{-5} mol litre^{-1}. Plasma concentrations of doxapram up to 5.2 µg ml^{-1} have been reported in man after i.v. infusions of doxapram [7]. This is in excess of 10^{-5} mol litre^{-1} and thus the concentrations used in this *in vitro* study are not greatly in excess of those achieved clinically.

The neuromuscular junction is a complex structure, and an agent may augment transmission in several ways [8]. The release of acetylcholine may be increased, or its breakdown inhibited. The agent may prolong transmitter–receptor binding or otherwise enhance ion flux. Alternatively, the agent may itself possess agonist activity. The lack of an effect on direct muscle stimulation suggests that any effect is likely to be at the motor endplate and not on the muscle membrane itself. Doxapram had no effect on cholinesterase in the concentrations which augment contraction and thus is unlikely to contribute to the observed effects. However, doxapram did inhibit acetylcholinesterase in concentration of 10^{-3} mol litre^{-1} and greater.

The experiments with the partially blocked neuromuscular junction preparations revealed an inhibitory component to the action of doxapram, which was more evident in the presence of agents which have significant activity at presynaptic receptors (β-bungarotoxin [4] and tubocurarine [9]). In these circumstances, the facilitatory effect of doxapram was reduced or lost. In contrast, facilitation of twitch tension by doxapram was still marked, even at moderate degrees of neuromuscular block, when the agent used possessed little or no presynaptic activity (α-bungarotoxin

[5]). This suggests that the facilitation of twitch tension by doxapram is a presynaptic effect at a site sensitive to tubocurarine and β-bungarotoxin. In the unblocked preparation, this masks an inhibitory component which is probably postsynaptic.

The neuromuscular blocking agents were chosen to have a range of activity from mainly presynaptic to selective postsynaptic block. Whilst the classifications of β-bungarotoxin as presynaptic [4] and α-bungarotoxin as postsynaptic [5] are well accepted, the relative positions of tubocurarine and pancuronium are more controversial. Most authors agree that both agents have both pre- and postsynaptic neuromuscular blocking activity [9]. Galindo [10] reported that curare had more prejunctional activity than pancuronium, whilst Blaber [11] disagreed, but observed that the concentration of agents used might be crucial. In higher concentrations, pancuronium affected the tissue response to doxapram in a manner similar to tubocurarine. However, lower concentrations were closer in character to the effects seen between α-bungarotoxin and doxapram. This could be explained in terms of the proposed concentration dependency of any presynaptic action of pancuronium.

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INHALATION ANAESTHETICS DECREASE CALCIUM CONTENT OF CARDIAC SARCOPLASMIC RETICULUM†

M. KATSUOKA AND S. T. OHNISHI

SUMMARY

In a Langendorff perfused rat heart model, caffeine was shown to have a negative inotropic effect similar to that of inhalation anaesthetics. Both inhalation anaesthetics and caffeine decreased calcium content of left ventricular muscle as measured by atomic absorption spectroscopy. Halothane 2.8% decreased left ventricular pressure by 75.4 (SEM 4.4)% and decreased the calcium content by 30%. Enflurane 5.1% decreased the pressure by 72.4 (6.0)% and decreased calcium content by 31%. Both halothane and enflurane decreased the calcium content of sarcoplasmic reticulum (SR) as measured by caffeine-induced calcium release. There was a high degree of correlation between the negative inotropic effect of inhalation anaesthetics and the decrease in calcium content of the SR ($r = 0.95$ for halothane, $r = 0.91$ for enflurane). These data suggest that inhalation anaesthetics increase the calcium permeability of cardiac SR, thereby decreasing the calcium content of SR, resulting in the negative inotropic effect.

It is known that general anaesthetics markedly reduce myocardial contractility [1–4]. In *in vitro* experiments, Price [5, 6] found that anaesthetic-induced reduction in contractile force of papillary muscle was antagonized by increasing calcium concentration in the bathing medium. One of the sites of action suggested by several investigators was the plasma membrane. Langer, Serena and Nudd [7] suggested that membrane surface-bound calcium plays a role in the contraction of cardiac muscle. Using a La^{3+} exchange technique, Ohnishi and colleagues [8] have shown that halothane reduces the amount of La^{3+}-exchangeable calcium in trabecular muscle in proportion to the decrease in contractility. They showed that the calcium binding of the preparation from cardiac plasma membrane lipoprotein was increased in the presence of general anaesthetics and ethanol [9].

While calcium bound to the plasma membrane may play a role in cardiac muscle contraction, the major site of interest is the sarcoplasmic reticulum (SR). Su and Kerrick [10] showed that halothane caused myocardial depression by inhibiting calcium uptake of SR in skinned fibres. Ohnishi [11, 12] found that both halothane and caffeine increased the calcium-induced calcium release from the SR. Using SR prepared from malignant hyperthermia-susceptible skeletal muscle, he found that both caffeine and halothane increased the calcium permeability of the SR [13]. We postulated that halothane may also increase calcium permeability of the cardiac SR, thereby decreasing the calcium content of the SR. In the present study, we have tested this hypothesis using a Langendorff perfused rat heart model. We measured both the total calcium content of the left ventricular muscle with atomic absorption spectroscopy and the amount of calcium ion released from the SR using a caffeine-induced calcium release method [14, 15].

MATERIALS AND METHODS

Langendorff perfusion model

Male Sprague–Dawley rats (weight 300–400 g) were anaesthetized by i.p. injection of pentobarbitone 50 mg kg^{-1}. The heart was removed quickly and immersed in ice cold Krebs–Henseleit bicarbonate solution (KHB solution; content

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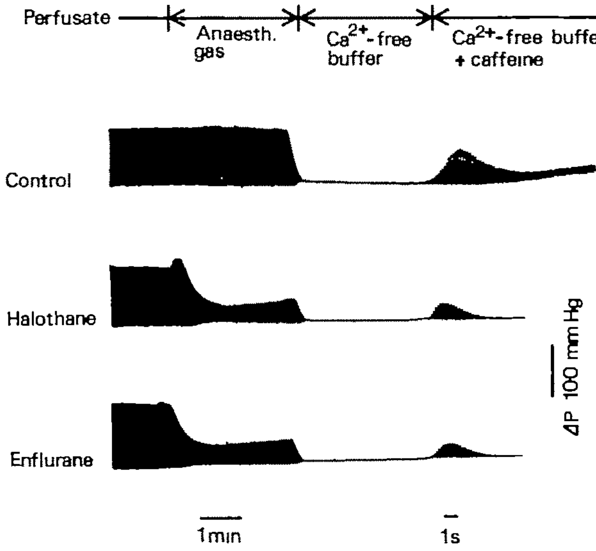

FIG. 1. Caffeine-induced contraction: Control (no addition); effect of 2.8% halothane and effect of 5.1% enflurane. The heart was perfused with inhalation anaesthetic (Anaesth.) for a few minutes and with Ca^{2+}-free buffer for 30 s, then with Ca^{2+}-free buffer containing caffeine 40 mmol $litre^{-1}$.

(mmol $litre^{-1}$): NaCl 118, KCl 4.7, $CaCl_2$ 1.25, $MgSO_4$ 1.25, KH_2PO_4 1.25, $NaHCO_3$ 24, glucose 15; pH adjusted to 7.4 when equilibrated with 5% carbon dioxide in oxygen at 37 °C). Extraneous tissue was removed and the aorta was cannulated on the perfusion apparatus. The left ventricular pressure was measured with a latex balloon connected to a Statham PB 23 transducer via a thin catheter. The balloon was inserted through the mitral valve and filled with water (volume 0.1–0.2 ml).

Relationship between left ventricular developed pressure (LVDP) and calcium content of the left ventricular muscle

The perfused heart was stimulated by electric pulses (10 V, 4–5 Hz, 10 ms duration). The KHB solution was changed to a KHB solution containing either caffeine or anaesthetic agents (the latter vaporized from a Dräger vaporizer and bubbled into the solution) and perfused for 10 min. The pressure decreased and reached a new plateau value within the first 5 min. The perfusing solution was changed to a Ca^{2+}-free KHB solution, and perfused for 1 min. The left ventricular muscle was cut into small pieces with scissors and homogenized with a polytron homogenizer (volume 10 ml). The homogenate was extracted with HCl 2 mol $litre^{-1}$ for 24 h with constant shaking. The suspension was centrifuged at 2000 rev min^{-1} for 10 min and the calcium concentration of the supernatant measured using a polarized Zeeman effect atomic absorption spectrophotometer (Hitachi Z-8000). The pellet was dissolved in 30% potassium hydroxide 10 ml and the protein concentration determined by a biuret method. Measurements were made in triplicates.

Estimation of calcium content of sarcoplasmic reticulum using caffeine

Calcium content of SR was measured by the procedures reported by Endo [14, 15] and Heide and colleagues [16], with a small modification. The heart was stimulated continuously (5 Hz). After equilibration with KHB solution for 15 min, the perfusing solution was switched to a Ca^{2+}-free KHB solution for 30 s then changed again, to a Ca^{2+}-free KHB solution containing caffeine 40 mmol $litre^{-1}$. Endo found that the calcium release at this high concentration of caffeine represented the amount of calcium left in the SR [14, 15]. Several contractions of the heart were observed (fig. 1) and the height of each contraction measured. It was assumed that the height of each contraction was related to calcium release from the SR and thus the summation of each contraction was regarded as the total calcium release from the SR in the presence of caffeine 40 mmol $litre^{-1}$.

Determination of anaesthetic concentration

Concentrations of halothane and enflurane from the respective vaporizers were determined by gas chromatography.

Data analysis

Each datum point was obtained from six separate experiments. Statistical analysis was performed using Student's t test.

RESULTS

Negative inotropic effects of caffeine, halothane and enflurane

When the heart was perfused with caffeine, diastolic pressure increased. Systolic pressure increased immediately and transiently, then decreased to a new plateau value which was smaller than the original one (negative inotropic effect). Similar changes were observed with both halothane and enflurane (fig. 2). LVDP was depressed by these agents in a dose-related manner (fig. 3). A reduction of 50% was produced by 1.8% halothane and 4.0% enflurane.

Effects of caffeine, halothane and enflurane on calcium content of left ventricular muscle

All these agents decreased the calcium content of left ventricular muscle as measured by atomic absorption spectrophotometry (fig. 4). When the heart was perfused with 2.8% halothane, 5.1% enflurane or caffeine 2 mmol litre^{-1}, the calcium content was decreased to 70.3 (9.5)% ($P < 0.05$), 69.4 (6.9)% ($P < 0.05$) and 56.1 (6.9)%

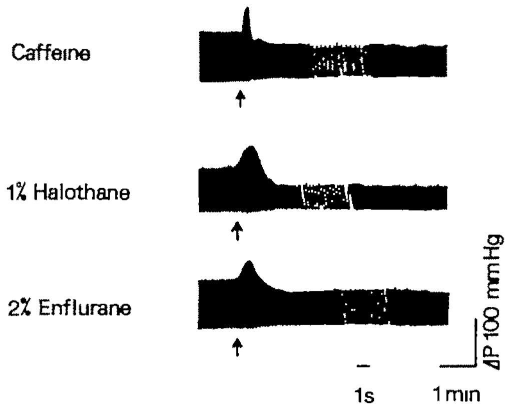

FIG. 2. Effects of caffeine 4 mmol litre^{-1}, 1% halothane and 2% enflurane on the left ventricular developed pressure (LVDP) of the isolated heart. Arrows indicate change in perfusate.

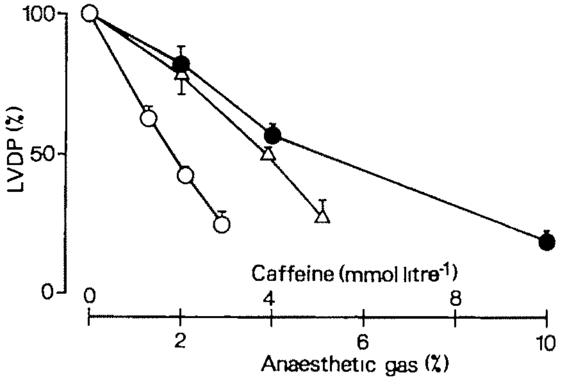

FIG. 3. Effects of caffeine (●), halothane (○) and enflurane (△) on the developed pressure (LVDP) expressed as a percentage of contraction perfused with buffer solution without agents (mean and SEM) ($n = 6$).

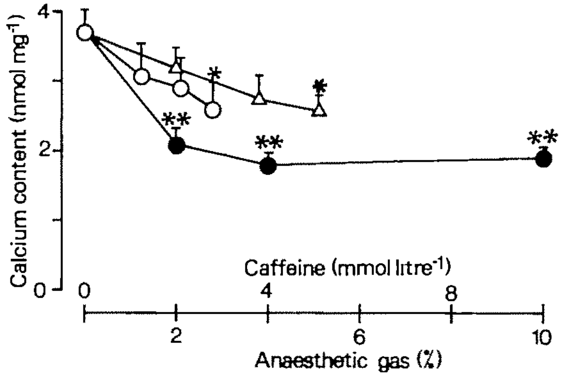

FIG. 4. Effects of caffeine (●), halothane (○) and enflurane (△) on calcium content of left ventricular muscle (mean and SEM) ($n = 6$) Calcium content was measured by atomic absorption spectrophotometry. Significant difference from normal perfusate: *$P < 0.05$; **$P < 0.01$.

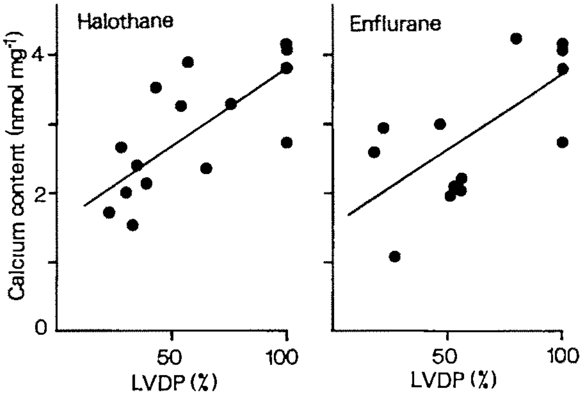

FIG. 5. Relationship between left ventricular developed pressure (LVDP) and calcium content in left ventricular muscle: effects of halothane ($r = 0.65$, $P < 0.05$) and enflurane ($r = 0.60$, $P < 0.05$).

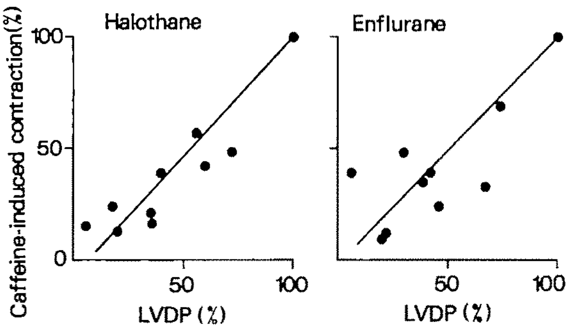

FIG. 6. Effect of halothane ($r = 0.95$, $P < 0.001$) and enflurane ($r = 0.91$, $P < 0.001$) on the relationship between left ventricular developed pressure (LVDP: percentage of control) and calcium content in the SR. Calcium content in the SR was measured as a caffeine-induced contraction and expressed as a percentage of control.

($P < 0.01$) of control, respectively. The relationship between LVDP and the calcium content of the left ventricular muscle was similar with halothane and enflurane ($r = 0.65$, $P < 0.05$ and $r = 0.60$, $P < 0.05$, respectively) (fig. 5).

Relationship between LVDP and calcium content in the SR

In this experiment, calcium content was estimated by caffeine-induced calcium release from the SR (fig. 1). There was a correlation between LVDP and calcium content of the SR ($r = 0.95$, $P < 0.001$ and $r = 0.91$, $P < 0.001$ for halothane and enflurane, respectively) (fig. 6).

DISCUSSION

Although inhalation anaesthetics are well known to reduce contractile force of the heart, the exact mechanism of action is not well understood. Using isolated skeletal muscle SR, it has been shown that inhalation anaesthetics, such as halothane and enflurane, stimulate calcium release from the SR [17]. It has also been demonstrated that both caffeine and inhalation anaesthetics increase the calcium permeability of SR membranes [11, 12] and it is well known that caffeine causes calcium release from the SR [14–17]. These findings suggest that there are close similarities between the mechanism of action of caffeine and that of inhalation anaesthetics on the SR, and that the mechanism of negative inotropism may be related to the stimulated calcium release from the SR. Using a Langendorff perfused heart model, we attempted to test this hypothesis.

First, we demonstrated that caffeine, a well known SR calcium releasing agent [14–17], has a negative inotropic effect on cardiac muscle (figs 2, 3). The action of caffeine and inhalation anaesthetics on the SR seemed to be similar: they caused an immediate increase in systolic pressure followed by a decrease, and they caused an increase in diastolic pressure (fig. 2). Second, we measured the calcium content of the left ventricular muscle using atomic absorption spectroscopy. Both inhalation anaesthetics and caffeine decreased the calcium content in a dose-related manner (fig. 4). Third, we used a method of estimating the calcium content of SR [14–16] and demonstrated that the tension developed in a muscle fibre in the presence of high concentrations of caffeine was related to the amount of calcium released from the SR. We applied the method to the heart by assuming that each contraction represented the amount of calcium released from cardiac SR. Caffeine-induced contraction of the heart was decreased with an increase in concentration of inhalation anaesthetic (fig. 1), suggesting, in agreement with results obtained by others [18, 19], that inhalation anaesthetics decrease the calcium content of the SR.

Several mechanisms may be involved in the negative inotropic effect of inhalation anaesthetics. They affect calcium binding of the plasma membrane [8, 9, 20] and the SR [10, 18, 19, 21–24], and the action potential [25, 26]. Our data suggest the possibility of a new mechanism involving the myocardial SR. As postulated previously [27], inhalation anaesthetics increase the calcium permeability of the cardiac SR (and of skeletal SR). This may cause a decrease in calcium content of the SR resulting in a decrease in the maximum developed tension of heart muscle,—that is, negative inotropism.

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ANTRODUODENAL MOTILITY, pH AND GASTRIC EMPTYING DURING BALANCED ANAESTHESIA: COMPARISON OF PETHIDINE AND FENTANYL

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Opioids have been shown to decrease motility in the stomach and to increase the tone of the antral part of duodenum [1]. Gastric emptying rate is delayed and the absorption rate of drugs administered by mouth is retarded [2, 3]. Furthermore, this group of drugs has been shown to cause some decrease in the secretion of hydrochloric acid in the stomach [4, 5].

The effects of opioid drugs on gastrointestinal motility, pH and gastric emptying rate in relation to anaesthesia are not fully elucidated, yet impeded motility and an increase in the volume of acid gastric contents increase the risk of pulmonary aspiration [6]. One study has suggested that gastric fluid production is minimal during anaesthesia, or that gastric emptying rate is normal or increased during non-abdominal surgery [7].

In previous studies, we have investigated the effects of general anaesthesia with enflurane and halothane on antroduodenal motility, pH and gastric emptying rate. It was found that both anaesthetics affected motility and delayed gastric emptying rate [8; Schurizek et al., in preparation].

This study was undertaken to evaluate the effects of pethidine and fentanyl on antroduodenal motility, pH and gastric emptying during barbiturate anaesthesia. Antroduodenal motility was measured by manometry [9–12], and gastric emptying was assessed using paracetamol absorption as an index [13, 14].

SUMMARY

In a randomized study of 22 patients, antroduodenal motility, pH and gastric emptying rate were measured during barbiturate anaesthesia with pethidine or fentanyl. Motility was measured by manometry and gastric emptying rate by the paracetamol absorption test. Anaesthesia reduced the duration of the interdigestive motility complexes with both analgesics ($P < 0.001$), mainly by a shortening of phase II ($P < 0.01$) The duration of phase II and III were shorter with pethidine, and pethidine reduced both the frequency and amplitudes of antral contractions during phase II ($P < 0.01$). Fentanyl affected only the amplitudes. The phase III variables assessed were unchanged, apart from a decrease in the velocity of propagation of the motility complexes with pethidine ($P < 0.01$). The gastric pH increased in both groups during and after operation ($P < 0.01$). Gastric emptying rate was normal in 82% with fentanyl and in 60% with pethidine. Motility in the recovery period approached, but did not reach, preoperative values. Balanced anaesthesia with pethidine and fentanyl seem to have minor influence on gastroduodenal motility and gastric emptying rate.

PATIENTS AND METHODS

We studied 22 patients without gastrointestinal symptoms or other systemic disease undergoing elective orthopaedic or plastic surgery not involving the abdomen. None of the patients was a regular user of drugs which are known to influence gastrointestinal motility or gastric pH.

The patients were allocated randomly to receive pethidine or fentanyl for analgesia during surgery.

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One patient receiving pethidine was excluded from the study because of displacement of the gastric tube during surgery.

Informed consent was obtained from all individuals before the study, which was approved by the local Ethics Committee.

Antroduodenal motility was recorded using a six-lumen polyvinylchloride tube with an external diameter of 4.7 mm (GIMK-14R7-250 A, William Cook, Europe A/S). Each lumen had an internal diameter of 0.7 mm and a side hole opening of 0.7 mm sited at various distances from the tip. Five lumina were used. The manometric assembly, complete with a pH electrode, was passed through a nostril and placed, under fluoroscopic control, so that the tip of the tube was near to the ligament of Treitz.

Side-openings at 2, 18, 34 and 42 cm from the tip of the tube were arranged in such a way that two were placed in the gastric antrum (A1 proximal and A2 distal) and two in the duodenum (D1 proximal and D2 distal). The lumina were perfused continuously with distilled water at a rate of 0.2 ml min^{-1} per channel, using a pressure infusor (Cook, Europe A/S). Intraluminal pressure was measured by strain gauge transducers (physiological pressure transducer, Gould-Statham) and recorded on a multi-channel paper chart recorder (Mingograf 805, Siemens Elema, Sweden).

A pH microelectrode (GK 2801-C, Radiometer, Copenhagen), calibrated with commercial buffer solutions (pH 1.09 and 4.01), was attached to the side of the manometric catheter between the two antral recording sites. Gastric antral pH was displayed continuously on a pH meter (pH-meter 75, Radiometer, Copenhagen) and recorded with the pressure activity on the paper chart recorder. All measurements were recorded via an interface on a multichannel tape recorder (TEAC XR-510) for later data compression and analysis.

The rate of gastric emptying was assessed by measuring serum concentrations of paracetamol after oral ingestion.

All patients were premedicated with diazepam 10–20 mg (Stesolid tablets) according to age and weight. Premedication was given at 6 a.m. and all investigations were started at 7 a.m. When the tube was positioned as described, preoperative antroduodenal motility and pH were measured.

Paracetamol was given immediately before induction of anaesthesia. Each patient received paracetamol approximately 20 mg kg^{-1} (whole and half Panodil tablets containing 500 mg with 20–40 ml of water) (table I). Venous blood samples were obtained for measurement of serum paracetamol concentrations at 15, 30 and 60 min and 1.5, 2.5, 3.5, 4.5, 5.5, 8, 12 and 24 h after ingestion. The serum was separated immediately and stored frozen.

Anaesthesia was induced with pethidine 30–60 mg or fentanyl 50–100 µg, and pancuronium 0.75–1.0 mg followed by thiopentone i.v. After tracheal intubation, anaesthesia was maintained with thiopentone in doses of 50 mg and 66% nitrous oxide in oxygen. Additional doses of pancuronium and pethidine or fentanyl were given as required. At the end of surgery residual neuromuscular block was antagonized with neostigmine 2.5 mg and atropine 1.0 mg. All patients were anaesthetized by the same staff.

Following anaesthesia, the patients were observed in the recovery room and analgesia (nicomorphine) given when needed. Antroduodenal motility and gastric pH were measured continuously except during transport to and from the operation room. When the patient had recovered fully from anaesthesia, the gastric tube was removed and the patient discharged to the surgical ward.

The recordings of motility and pH were assessed manually and each phase of interdigestive motility complex (IDMC) was identified and analysed separately. The IDMC has three phases. During phase I, which lasts 30–45 min, few or no contractions occur. Phase II has intermittent contractions and lasts 30–90 min (the average frequency being 0–12 per 5 min in the gastric

TABLE I *Age, weight, sex distribution and doses of premedication (diazepam) and paracetamol (medians (range))*

	Age (yr)	Weight (kg)	Sex ratio (F:M)	Diazepam (mg kg^{-1})	Paracetamol (mg kg^{-1})
Pethidine	34 (21–66)	68 (62–95)	7:3	0.27 (0.21–0.32)	20.0 (18.6–21.7)
Fentanyl	39 (18–71)	61 (44–78)	7:4	0.27 (0.19–0.34)	20.5 (18.4–22.7)

antrum, and 2–38 per 5 min in duodenum, the amplitudes being 15–180 mm Hg and 15–100 mm Hg, respectively). The frequency of contractions increases during phase II, culminating in the onset of phase III which is characterized by regular propagating contractions (average frequency 3 per 1 min in the gastric antrum and 10–12 per 1 min in duodenum; amplitudes 15–90 mm Hg and 15–30 mm Hg, respectively). The duration of phase III is 5–15 min and approximately 50% has an antral component (complete phase III), the remainder beginning in the proximal part of the duodenum ("incomplete" phase III) [11–15].

An IDMC was defined as the motility pattern from the beginning of one phase III to the beginning of the next.

Motility was assessed as follows. For phase I the duration was noted. Phase II was assessed for duration and frequency and amplitude of contraction, and a motility index (frequency × amplitude) was calculated. Each phase II was divided into 5-min intervals for which frequency and average amplitude were calculated for each recording site. Each phase III was assessed for duration, frequency of contraction, amplitudes and velocity of propagation (cm min^{-1}). The velocity of propagation was measured from A2 to D1 and from D1 to D2 and an average calculated. Both complete and incomplete phases III were noted.

The motility data for each phase at each recording site in the pre-, per- and postoperative observation periods were pooled and compared.

The median of the highest and lowest antral pH was calculated for each 5-min epoch.

Serum paracetamol concentrations were measured by high pressure liquid chromatography [16]. Paracetamol absorption was assessed from the serum concentrations at each sampling time, the peak paracetamol concentrations (*C*max), the time to reach the peak (*t*max) and the area under the serum concentration curves (AUC). Patients reaching *C*max during anaesthesia were classified as fast absorbers. Patients not fulfilling this criterion were classified as slow absorbers.

In comparing doses of opioid, equianalgesic doses were used [17].

Statistical analysis was carried out with non-parametric two-way analysis of variance, Kruskall–Wallis, Mann–Whitney, Fisher's exact and Spearman rank correlation tests, $P < 0.05$ being considered significant. When a statistical difference using the two-way analysis of variance and the Kruskall–Wallis test was found, Dunn's test was applied. Values are given as medians with quartile spans or range.

RESULTS

The two groups were similar with respect to demographic data, dose of premedication and paracetamol dosage (table I).

One hundred and nineteen IDMC (three to nine in each patient) were observed, the pre-, per- and postoperative recording times being medians of 27.5 (17–168) min, 185 (110–250) min and 125 (90–240) min with pethidine and medians of 99 (22–165) min, 180 (75–325) min and 190 (100–300) min with fentanyl. The numbers and the duration of the IDMC, phase I, II and III before, during and after anaesthesia are shown in table II.

The pattern of motility and antral pH did not differ between groups in the preoperative period. None of the patients had an abnormal pattern of motility and none was anacidic (fig. 1). The velocity of propagation during phase III was 6.6 (3.9–11.4) cm min^{-1} in the pethidine group and 8.0 (3.9–12.2) cm min^{-1} in the fentanyl group. Forty-four percent of the preoperative phase III were complete.

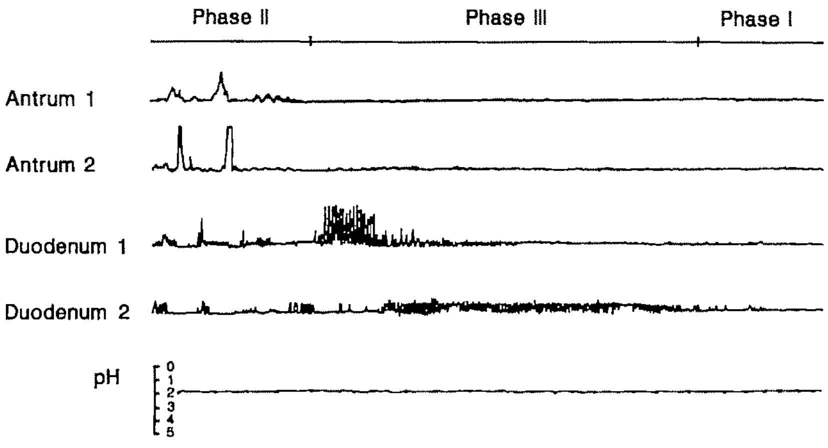
Anaesthesia

Induction, maintenance and total doses of thiopentone and opoids are shown in table III.

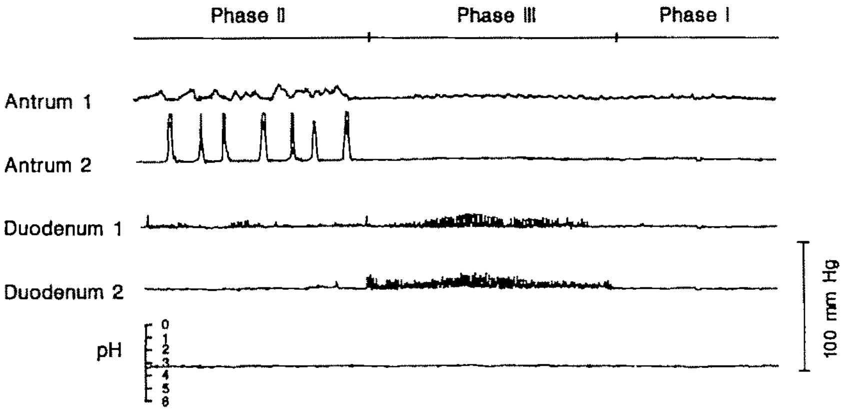
Anaesthesia was induced in phase II in all patients except two, in whom induction was in phase I. The injection of both opioids provoked in all patients, after a median of 2.5 (1–6) min (pethidine group) and a median of 2.75 (1–5) min (fentanyl group), a burst of propagating activity indistinguishable from phase III of the IDMC. Three patients in the pethidine group and seven in the fentanyl group had both antral and duodenal contractions.

Although the cycle duration varied considerably between and within subjects, the duration of the IDMC was reduced ($P < 0.001$) mainly by a reduction in phase II ($P < 0.01$). The duration of phase I was shorter and the duration of phase II and III were longer with fentanyl ($P < 0.01$) (table II).

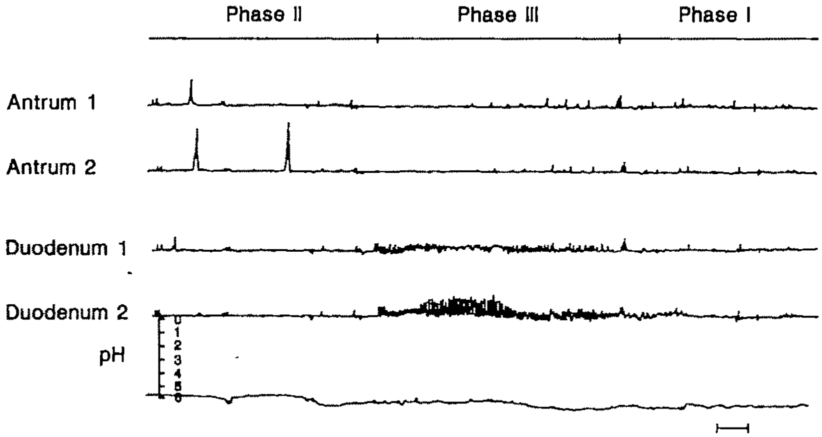
The changes in motility during phase II were small (figs 2, 3). Pethidine reduced the frequency (A2) ($P < 0.01$) and the amplitudes of contractions in antrum (A1, A2) ($P < 0.01$). Fentanyl



Preoperative motility



Peroperative motility



Postoperative motility

FIG. 1. Antroduodenal pressure activity and pH in the pre-, per- and postoperative periods.

TABLE II. *Duration of the IDMC, phase I, phase II and phase III in the pre-, per- and postoperative period (medians (quartile spans)).* n = *Number of observations.* *$P < 0.05$ *(two-way analysis of variance)*; †P < 0 05 *(Dunn's test)*

	Before op. (min)	During op. (min)	After op. (min)
IDMC			
Pethidine	94 (64–100)	28.5 (20–35)*	34 (21–47)*
	($n = 5$)	($n = 54$)	($n = 8$)
Fentanyl	100 (89–123)	36.0 (21–47)*†	68 (53–121)†
	($n = 4$)	($n = 41$)	($n = 7$)
Phase I			
Pethidine	15 (8–28)	10 (2–16)	3 (1–38)
	($n = 8$)	($n = 60$)	($n = 14$)
Fentanyl	12 (4–25)	4 (0–12)*	21 (5–49)†
	($n = 5$)	($n = 48$)	($n = 21$)
Phase II			
Pethidine	51 (33–160)	6 (0–10)*	20 (0–38)*
	($n = 6$)	($n = 57$)	($n = 9$)
Fentanyl	98 (74–140)	13 (4–30)*†	20 (10–31)*
	($n = 7$)	($n = 44$)	($n = 14$)
Phase III			
Pethidine	6 (2.4–10.7)	6.7 (4–7 4)	5 (3.5–7.4)
	($n = 8$)	($n = 63$)	($n = 16$)
Fentanyl	10 (2.6–11.9)	7.75 (6–11.2)†	3 (2–6.6)
	($n = 6$)	($n = 52$)	($n = 22$)

reduced the antral amplitudes (A2) ($P < 0.01$) and caused a discrete decline in the frequency of contractions in the proximal duodenum ($P = 0.05$). The motility index in antrum was unchanged, but increased in duodenum in both groups (D1 in the pethidine group and in D2 in the fentanyl group) ($P < 0.01$).

Most of the phase III variables assessed were unchanged during anaesthesia. More phase III had an antral component in the fentanyl group (59% *v.* 28%) ($P < 0.02$). Only few phase III were non-propagating: five of the pethidine group and seven of the fentanyl group. The velocity of propagation was reduced in the pethidine group (3.7 (2.6–30) cm min^{-1} ($P < 0.05$)), but not in the fentanyl group (9.9 (2.8–48) cm min^{-1}).

TABLE III. *Induction, maintenance and total doses of thiopentone and opioid in the two groups of patients (medians (range))*

	Pethidine group	Fentanyl group
Induction		
Thiopentone (mg kg^{-1})	7.25 (5.7–12.5)	6.75 (4.0–11.8)
Opioid (mg kg^{-1})	0.80 (0.6–1.2)	
(µg kg^{-1})		1.67 (1.3–2.3)
Maintenance		
Thiopentone (mg kg^{-1} h^{-1})	1.24 (0.5–2.2)	1.05 (0.2–2.0)
Opioid (mg kg^{-1} h^{-1})	0.45 (0.3–0.6)	
(µg kg^{-1} h^{-1})		1.42 (0.4–1.8)
Total		
Thiopentone (mg)	750 (400–800)	675 (450–800)
Opioid (mg)	155 (120–190)	
(µg)		350 (200–450)

The ability of the opioids to provoke phase III activity was moderately depressed during anaesthesia. Apart from the induction doses, 47 doses of pethidine and 53 of fentanyl were given. Of these, 30% (pethidine) and 32% (fentanyl) were not followed by phase III activity, and this was different from the response during induction ($P < 0.05$).

Anaesthesia suppressed the secretion of hydrochloric acid in both groups, but significantly more in the fentanyl group ($P < 0.01$) (table IV).

No change in motility occurred following injection of thiopentone, pancuronium or neostigmine–atropine.

Recovery

Eleven patients received nicomorphine in doses of 2 mg i.v. in the postoperative period (four with pethidine; seven with fentanyl). The injections provoked phase III activity in eight subjects.

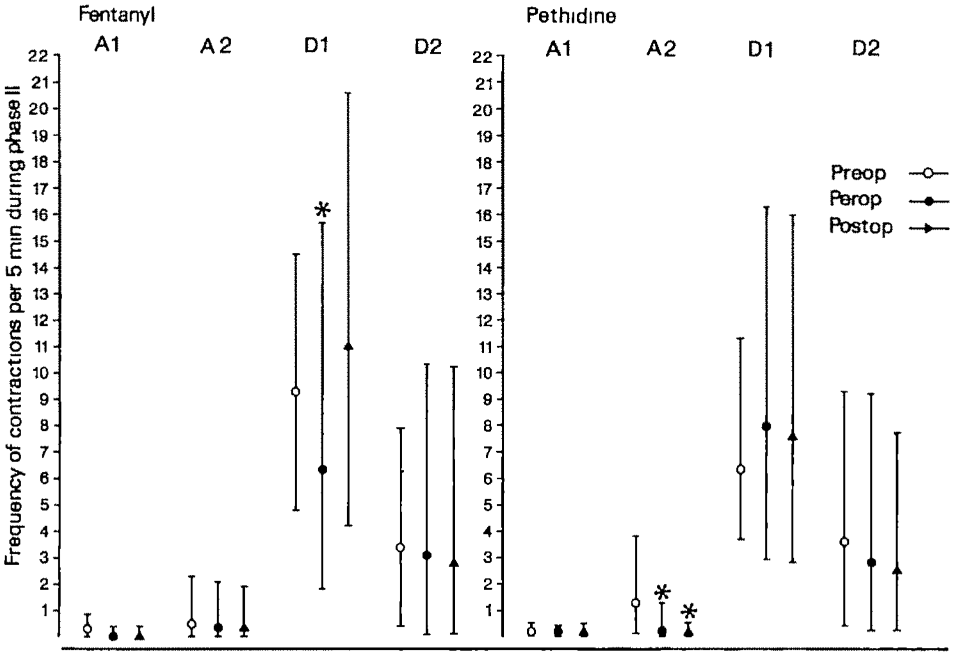


FIG. 2. Frequency of contractions per 5 min in the two groups during the pre-, per- and postoperative periods (medians with quartile spans). *$P < 0.01$ (two-way analysis of variance).

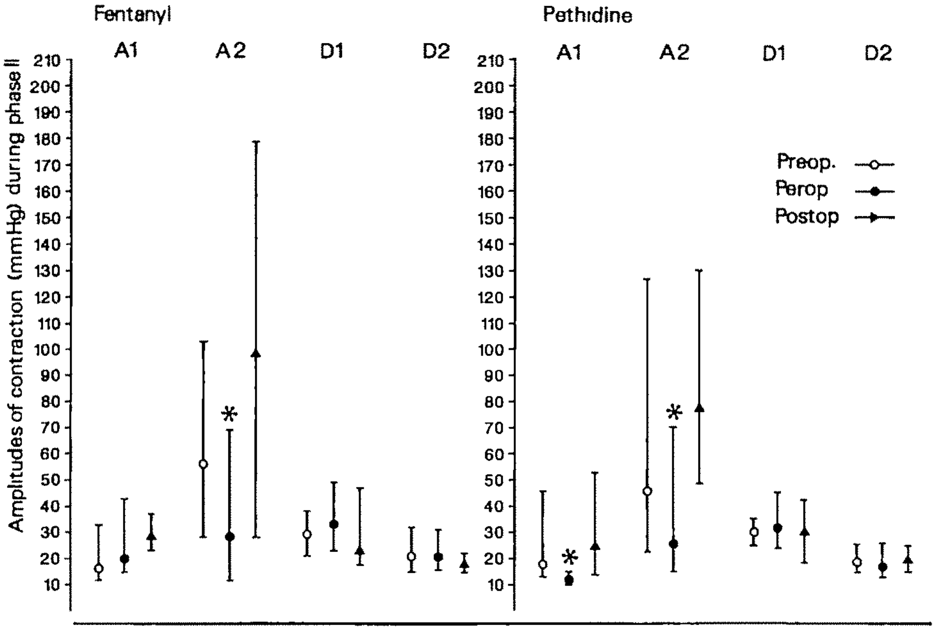


FIG. 3. Amplitudes of contractions in the pre-, per- and postoperative periods (medians with quartile spans). *$P < 0.01$ (two-way analysis of variance).

TABLE IV *pH Values in phase II during the pre-, per- and postoperative observation periods (median) (range)).* *P < *0.05 (two-way analysis of variance)*; †P < *0.05 (Dunn's test)*

	Before op.	During op.	After op.
Pethidine group			
pH min	1.5 (1.3–1.9)	2.3 (2.8–3.4)*	3.4 (2.1–6.2)*
pH max	1.7 (1.5–2.0)	2.6 (2.0–3.6)*	3.5 (2.5–6.2)*
Fentanyl group			
pH min	1.7 (1.0–2.4)	3.2 (1.6–6.2)*†	5.6 (3.0–6.2)*
pH max	2.0 (1.4–2.8)	3.4 (1.7–6.2)*	5.8 (3.0–6.6)*

TABLE V. *tmax, Cmax, AUC (24 h) and antral activity in patients reaching tmax during anaesthesia and in patients reaching tmax during the recovery period (medians (range))*

	Pethidine group ($n = 10$)		Fentanyl group ($n = 11$)	
	Anaesthesia ($n = 6$)	Recovery ($n = 4$)	Anaesthesia ($n = 9$)	Recovery ($n = 2$)
tmax (h)	0.6 (0.25–1.5)	8 (8–12)	0.25 (0.25–1.0)	4.5 (–)
Cmax (μg ml^{-1})	11.1 (2.0–22.4)	4.5 (1.9–8.8)	7.0 (3.8–19.0)	1.8 (1.4–2.0)
AUC	3156 (577–3863)	2566 (1425–4524)	2347 (1624–3276)	615 (188–1143)
Antral activity	+	–	+	–

The duration of phase II remained depressed in the postoperative period in both groups ($P < 0.01$) (table II). Phase I shortened with pethidine.

A further decrease in the frequency of antral contractions during phase II was seen in the pethidine group (A2) ($P < 0.05$). The antral amplitudes and the motility index increased in both groups (A2) ($P < 0.01$). Duodenal phase II recordings were unchanged (figs 2, 3).

Phase III parameters were unaffected in the recovery period. Thirty-eight phase III were seen; eight were non-propagating, but only one of these occurred in relation to injection of opioid.

The secretion of hydrochloric acid remained depressed ($P < 0.01$) (table IV).

A correlation was found in both groups between duration of anaesthesia and recovery time (Spearman Rho 0.633 (pethidine) and 0.189 (fentanyl)).

Gastric emptying rate

Peak concentrations of paracetamol were observed during anaesthesia in six patients with pethidine and nine with fentanyl. Gastric emptying rate was faster with fentanyl ($P = 0.07$). Four patients in the pethidine group and two in the fentanyl group had delayed gastric emptying. The AUC at 24 h did not differ between the groups of fast and slow absorbers in each group (table V).

All patients who had peak concentrations of paracetamol during anaesthesia exhibited a pattern of motility characterized by episodes of antral contractions during phases II and III, while no antral contractions were seen in the group of slow absorbers.

DISCUSSION

Gastric emptying rate is normal before anaesthesia for elective surgery [18, 19] when opioids are not used for premedication [20, 21]. A correlation has been found between delayed gastric emptying and administration of opioid drugs after operation [22]. The present study demonstrates that the effects of opioids on gastrointestinal motility and gastric emptying is suppressed during balanced anaesthesia with barbiturates.

Oral administration of diazepam causes a reduction in the acidity of stomach contents, an increase in amplitudes of contraction and tends to increase gastric emptying rate [23].

Few IDMC were seen in the preoperative period, but the duration and the motility variables were similar to those in the healthy volunteers [11, 23].

In a previous study we have shown that 82 % of healthy, non-anaesthetized subjects attain peak plasma concentrations of paracetamol within 90 min of oral ingestion and that there is a close connection between gastric emptying rate and antral activity [11]. This study confirms the association between antral contractions, even with smaller amplitudes, and the rate of gastric emptying. Furthermore, the tone in the antral part of duodenum was unaffected. Gastric emptying rate was close to normal in the present study, although it tended to be faster in the fentanyl group in association with greater antral activity and normal velocity of propagation.

Thiopentone has been found to have variable effects on gastrointestinal motility. In one study the only effect noted was a reduction in velocity of propagation of the complexes by 20 %, while in another there was a transient stimulation of mechanical activity in duodenum [24, 25]. Hypnotic doses of barbiturates reduce motility in fasted human subjects, probably by depressing the vagus [26]. A similar phenomenon occurs during physiological sleep, where a reduction in phase II motility occurs [27, 28]. In our study, a decrease in the duration of the IDMC and especially phase II was found.

The administration of opioids may have contributed to the reduction in duration of the IDMC as these drugs have been shown to produce a dose-dependent increase in frequency of occurrence of the IDMC and in the mean time required for the IDMC to traverse the small intestines [29]. It is possible that opioids activate the IDMC via pathways from the central nervous system to the gut but, in general, they cause an increase in basal luminal pressure and stimulate segmental phase III, resembling activity [30]. No increase in the basal luminal pressure was seen in this study and only few phase III were segmental.

Opioids may decrease catecholamine concentrations via analgesic mechanisms, or increase the concentrations by activation of separate central nervous system pathways [31]. The effects of opioids on gastrointestinal motility may be explained partly by the latter action, as dopaminergic substances are known to inhibit gastric motility and delay gastric emptying [1]. During barbiturate anaesthesia, an increase in catecholamine concentrations is prevented [32] and this might explain why pethidine and fentanyl did not delay gastric emptying during anaesthesia.

The secretion of hydrochloric acid decreased during anaesthesia, particularly in the fentanyl group. Opioids may affect the sensitivity of the parietal cell directly, or indirectly by inhibiting release of acetylcholine from the vagal nerve ending. It is more probable that the inhibition of acid secretion was a result of central effects, as motility was relatively unaffected—an effect most pronounced with fentanyl [5].

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EFFECT OF ATRACURIUM AND LAUDANOSINE ON THE RELEASE OF ^{3}H-NORADRENALINE

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Atracurium is a non-depolarizing neuromuscular blocking drug [1] which is metabolized primarily to laudanosine via Hofmann elimination [1–3]. Laudanosine has a substantially longer half-life [2, 4] than atracurium and it may be expected to accumulate when used in intensive therapy. Although atracurium has minimal cardiovascular effects [5, 6], concern has been expressed about the possible side effects of its metabolite, laudanosine [2]. Atracurium has been shown to produce slight tachycardia [7], and EEG arousal [8] and in high doses laudanosine produces stimulation and convulsions in animals [8–11]. Therefore it seemed appropriate to study the effects of atracurium and laudanosine on release of ^{3}H-noradrenaline (^{3}H-NA) from isolated guineapig right atrium, a method shown to be useful [12, 13] for studying the effect of neuromuscular blocking agents and for drawing conclusions on their cardiovascular effect.

It is known from *in vitro* experiments that, in the absence of plasma enzymes [14], atracurium breaks down by Hofmann elimination to form laudanosine and other metabolites, and that the rate of reaction increases with pH and depends on temperature [14, 15]. Therefore we studied the effect on ^{3}H-NA release of atracurium kept at 4 °C and 37 °C before use, and we also measured the production of laudanosine, by HPLC [16].

(Preliminary data have been presented elsewhere [17].)

SUMMARY

We examined the effects of atracurium and its breakdown product, laudanosine, on resting and stimulation-evoked release of ^{3}H-noradrenaline (^{3}H-NA) from sympathetic axon terminals of isolated right atria of guineapigs. Both atracurium 1–100 µmol litre^{-1} and laudanosine 1–50 µmol litre^{-1} enhanced the release of ^{3}H-NA evoked by field stimulation (2 Hz, 24 stimuli), but did not affect resting release. When the production of laudanosine from atracurium was inhibited by maintaining the atracurium solution at 4 °C, atracurium did not enhance the release of ^{3}H-NA as occured when it was kept at 37 °C. However, atracurium antagonized the inhibitory effect of oxotremorine on release of ^{3}H-NA, whereas laudanosine did not. These data suggest that atracurium possesses an antimuscarinic effect. Its metabolite, laudanosine, in concentrations which would be expected following prolonged administration of atracurium, produced a marked increase in release of ^{3}H-NA. This effect of laudanosine may explain some of the unwanted effects seen following administration of atracurium.

METHODS

Isolated right atrium

Guineapigs of both sexes (weights 300–500 g) were studied. The right atria were incubated in modified Krebs' solution containing 1-(7,8)-^{3}H-noradrenaline (^{3}H-NA) (185 KBq ml^{-1}, 1.55 TBq mmol^{-1} sp. act., Amersham) at 37 °C for 40 min. During incubation the medium was bubbled with 5% carbon dioxide in oxygen. To facilitate ^{3}H-NA uptake, the preparations were stimulated with supramaximal impulses of 1 ms duration at 1 Hz for 40 min via two platinum electrodes. After incubation, the atria was washed several times

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with Krebs' solution and suspended in 2.0-ml organ baths. The preparations were superfused (1 ml min^{-1}) for 90 min with Krebs' solution containing ascorbic acid 3×10^{-3} mol $litre^{-1}$ and sodium-EDTA 10^{-5} mol $litre^{-1}$ at 37 °C and the effluent was discarded. Subsequently, 3-min fractions were collected and the radioactivity in each fraction was assayed by liquid scintillation spectrometry (Packard Tri-Carb 4530). In addition, the tissues were blotted with filter paper, weighed, homogenized in tissue solubilizer, and the radioactive content of a 100-µl aliquot of the homogenate assayed for radioactivity. The release of radioactivity expressed in Bq g^{-1} was determined and the fractional release was calculated.

Electrical stimulation

The tissues were stimulated via platinum electrodes, one above and the other below the suspended atrial strip. Supramaximal (10 V cm^{-1}) field stimuli (1 ms at 2 Hz for 2-min periods (240 stimuli), Grass 88 stimulator) were applied at 9 min (S_1), 27 min (S_2), 45 min (S_3), 63 min (S_4) and 81 min (S_5). In the absence of drugs, the ratios of evoked release of hydrogen-3 (S_2/S_1, S_3/S_2, S_4/S_3, S_5/S_4) were constant. Consequently, the effects of atracurium besylate (Borroughs Wellcome Co.) and laudanosine (Aldrich) on the evoked release of hydrogen-3 could be assessed by comparing the corresponding ratios in the absence (control) and presence of drugs. An increase in the ratio S_{n+1}/S_n indicated enhanced release of ^{3}H-NA, a decrease indicated reduced release.

Determination of noradrenaline

Noradrenaline was measured by high pressure liquid chromatography (HPLC) with electrochemical detection. The system was composed of a Waters pump, U6K sample injector, a uBondapak C18 column (300 × 3.9 mm), an LC4B amperometric detector (BioAnalytical Systems Inc.) with glassy carbon electrode set at a potential of +0.72 V and Waters 730 Data Module. The mobile phase consisted of sodium acetate/perchloric acid 0.05 mol $litre^{-1}$, pH 4.8, containing Na_2EDTA 0.26 mmol $litre^{-1}$ and heptane sulphonic acid 4.5 mmol $litre^{-1}$. The mobile phase was filtered through a 0.45-µm Millipore filter, degassed under vacuum and 7 % acetonitrile added. The flow rate was 1.0 ml min^{-1}. Noradrenaline standards were diluted in perchloric acid 0.2 mol $litre^{-1}$ – ascorbic acid 0.11 mmol $litre^{-1}$ solution from a 1-mol $litre^{-1}$ stock solution stored frozen in hydrochloric acid 0.1 mol $litre^{-1}$.

HPLC and radiochemical detection

For separation of ^{3}H-NA from its metabolites, 20 µl of the supernatant and 20-µl aliquots of the samples collected during both resting period and electrical stimulation were injected onto the HPLC column, and the radioactivity in 1-ml min^{-1} fractions of the HPLC effluent was estimated [18].

Determination of laudanosine

The method of Simmonds [19] was used to determine the concentration of laudanosine in the Krebs' solution. Briefly, laudanosine was separated by HPLC with a Partisil 10 column at 60 °C, and measured with a Hitachi 650-10LC fluorescence detector set at 280 nm (excitation) and 320 nm (emission). The mobile phase consisted of acetonitrile/sodium sulphate 60 mmol $litre^{-1}$ (60:40) in sulphuric acid 50 mmol $litre^{-1}$. The flow rate was 2 ml min^{-1}. N-methyl laudanosine was used as an internal standard. The sensitivity of this method was laudanosine 5 ng ml^{-1}. There were no interfering peaks, and laudanosine and atracurium were separated completely.

Effect of temperature

Solutions of atracurium and of laudanosine in Krebs' solution were preincubated for 30 min at 4 °C or 37 °C. The concentration of laudanosine in the atracurium solution was measured immediately, by HPLC. Effects of all four solutions on release of noradrenaline were measured at 37 °C.

Mode of action of atracurium and laudanosine

To test the possible antimuscarinic activity of atracurium or laudanosine, we added oxotremorine (Aldrich) 0.5 µmol $litre^{-1}$ (a drug known to have an inhibitory effect on release of noradrenaline) to the perfusing Krebs' solution 12 min before S_3 stimulation and retained it through subsequent stimulations. We measured changes in its inhibitory effect produced by laudanosine 10 µmol $litre^{-1}$ and by atracurium 2 or 10 µmol $litre^{-1}$, and compared them with changes produced by pancuronium (Organon) 2 µmol $litre^{-1}$, which has a known antimuscarinic effect.

In similar experiments, atropine sulphate (Aldrich) 1 µmol $litre^{-1}$ was added to the perfusing solution instead of oxotremorine, and the effects of histamine hydrochloride (Aldrich) 0.1 and 1.0

μmol litre^{-1}, an H_1-receptor blocker, pyrilamine maleate (Sigma) 1 μmol litre^{-1}, and an H_2-receptor blocker, cimetidine (Sigma) 3.5 μmol litre^{-1}, on ^{3}H-NA release from guineapig atrium, and their influence on the effect of atracurium, were studied.

The possible alpha-2 adrenoceptor blocking activity of laudanosine was investigated by comparing the inhibitory activity of clonidine hydrochloride (Bohringer Ingelheim Ltd) (log concentrations from −8.7 to −4.2 mol litre^{-1}) on release of noradrenaline in the presence and absence of laudanosine. In addition, we studied the effect of laudanosine 1–50 μmol litre^{-1} on 0.1-Hz stimulation-evoked contractions of rat vas deferens in the presence and absence of the alpha-2 adrenoceptor blocker, xylazine.

In all these studies, the neuromuscular blocking drugs were added to the Krebs' solution between stimulations S_3 and S_4, other test drugs having been added before S_3 (usually 12 min before). There was a delay of 2 min between addition of a drug to the reservoir and its arrival in the organ bath. Effects of drugs are expressed as ratios: S_{n+1}/S_n.

Statistics

Statistical significance was assessed by one-way analysis of variance (ANOVA) followed by Dunn's test and paried *t* test. The values are mean (SEM).

RESULTS

After 40 min loading followed by 90 min washout, the tissue contained 2.4 (0.2) × 10^6 Bq g^{-1} (mean (SEM)) radioactivity. Of this, 2.0 (0.2) × 10^6 Bq g^{-1} was found to be ^{3}H-NA. As the noradrenaline content of the tissue was 45.8 (1.3) nmol g^{-1}, 3.0 (0.1)% of the noradrenaline taken up by the tissue was labelled. At rest during 3-min collection period, 0.29 (0.01)% of the total radioactivity was released (table I). The resting release at the beginning and end of experiments was 6679 (380) and 6492 (398) Bq g^{-1} (number of experiments, *n* = 10–10), indicating that the release was constant. In response to field stimulation (2 Hz, 240 stimuli) 0.90 (0.04)% of the radioactivity present in the tissue at the time of stimulation was released (*n* = 10). The evoked release was constant: the ratios between the amounts of radioactivities released by consecutive stimulations (S_2/S_1, S_3/S_2, S_4/S_3) were 0.97 (0.02), 0.99 (0.02), and 0.96 (0.02), respectively. These values did not differ significantly. During the entire experiment only 16.0 (0.70)% (*n* = 10) of the total radioactivity taken up and stored was released.

Effect of atracurium and laudanosine on ^{3}H-noradrenaline release

Although neither atracurium nor laudanosine affected the release of ^{3}H-NA at rest, they did enhance the stimulation-evoked release. The effect of atracurium and laudanosine on ^{3}H-NA release was concentration dependent (table I, figs 1, 2). The action of atracurium on stimulated ^{3}H-NA release increased with time (fig. 2), whereas the effect of laudanosine was maximal within 12 min. Direct evidence was obtained with HPLC that, at 2-Hz stimulation, 72.3 (4.8)% (*n* = 4) of the total radioactivity released was ^{3}H-NA. When atracurium 50 μmol litre^{-1} 78.6 (3.9)% (*n* = 4) or laudanosine 10 μmol litre^{-1} 81.1 (6.8)% (*n* = 4) was added to the perfusion fluid, ^{3}H-NA accounted for similar proportions of the hydrogen-3 (78.6 (3.9)% and 81.1 (6.8)%, respectively).

TABLE I. *Effect of atracurium and its breakdown product laudanosine on stimulation-evoked release of ^{3}H-noradrenaline from isolated right atrium* (n = 4–4). *In controls no drug was added between S_2 and S_3. † Difference between S_2/S_1 and S_3/S_2 (paired* t *test). All values of S_3/S_2 with drugs different from control* (P < 0.01, *ANOVA test*)

Drug	S_2/S_1 (no drug)	S_3/S_2 (with drug)	*P*†
Control	0.97 (0.02)	0.99 (0.02)	ns
Atracurium 10 μmol litre^{-1}	0.92 (0.02)	1.18 (0.06)	< 0.01
Atracurium 50 μmol litre^{-1}	0.96 (0.04)	1.32 (0.17)	< 0.01
Laudanosine 1 μmol litre^{-1}	1.00 (0.02)	1.21 (0.03)	< 0.01
Laudanosine 10 μmol litre^{-1}	0.95 (0.01)	2.17 (0.02)	< 0.001
Laudanosine 50 μmol litre^{-1}	0.94 (0.02)	4.58 (0.14)	< 0.001

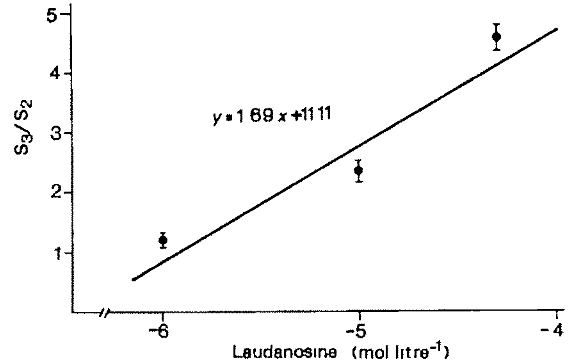

FIG. 1. Effect of laudanosine on release of ^{3}H-noradrenaline evoked by stimulation (2 Hz, 240 stimuli) of the isolated right atrium of guineapig heart, expressed as S_3/S_2 (ratio of ^{3}H-noradrenline released by second and third electrical stimuli).

Mode of action of atracurium

Effect on muscarinic receptors. The release of noradrenaline from sympathetic axon terminals is controlled by acetylcholine via presynaptic muscarinic receptor stimulation [12, 13, 20]. Some non-depolarizing neuromuscular blocking drugs (pancuronium, gallamine) possess antimuscarinic effects and are thus able to antagonize the cholinergic control of noradrenaline release [12, 13]. Both pancuronium and atracurium abolished the inhibitory effect of oxotremorine on ^{3}H-NA release (table II). In contrast, laudanosine 10 µmol litre^{-1} did not antagonize the effect of oxotremorine. This finding indicates that, while atracurium exerted an antimuscarinic activity, laudanosine did not.

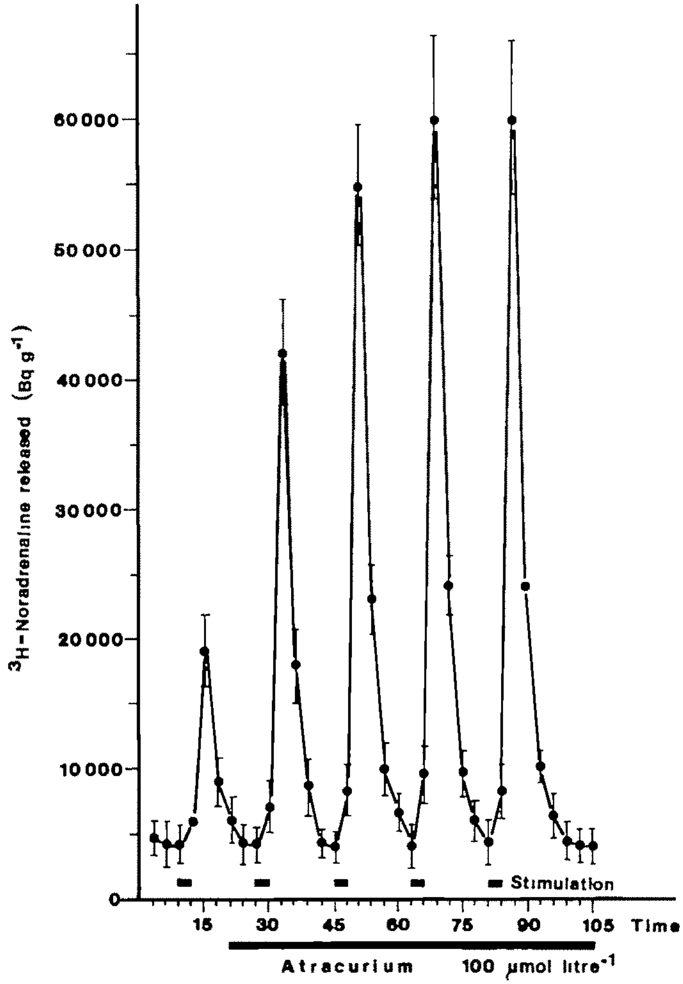

FIG. 2. Effect of atracurium 100 µmol litre^{-1} on release of ^{3}H-noradrenaline (mean, SEM) evoked by stimulation of the isolated right atrium of guineapig heart. Stimulation 2 Hz (240 stimuli). Average of four identical experiments.

TABLE II. *Comparison of the effects of laudanosine, atracurium and pancuronium on ^{3}H-noradrenaline release evoked by electrical stimulation* (n = 4–4). *Oxotremorine was added to the perfusing Krebs' solution 12 min before S_3; test drugs were added between S_3 and S_4.* * *Significant difference* ($P < 0.05$) *from control values, same column;* † *S_4/S_3 compared with S_3/S_2*

Drug	Temperature of drug (°C)	S_2/S_1 (no drug)	S_3/S_2 with oxotremorine (no drug)	S_4/S_3 with oxotremorine + drug	*P*
Control	37	0.97 (0.03)	0.24 (0.03)	0.91 (0.08)	ns
Laudanosine 10 μmol litre^{-1}	37	0.94 (0.03)	0.11 (0.01)*	1.39 (0.22)	< 0.05
Atracurium 10 μmol litre^{-1}	37	0.99 (0.03)	0.19 (0.02)*	4.01 (0.29)*	< 0.05
Atracurium 2 μmol litre^{-1}	37	0.95 (0.05)	0.22 (0.05)*	1.85 (0.05)*	< 0.05
Pancuronium 2 μmol litre^{-1}	37	1.00 (0.02)	0.21 (0.03)*	4.26 (0.41)*	< 0.05
Control	4	0.95 (0.02)	0.22 (0.02)*	0.93 (0.05)	ns
Atracurium 10 μmol litre^{-1}	4	0.97 (0.05)	0.16 (0.04)*	3.87 (0.16)*	< 0.05

TABLE III. *Effect of atracurium and laudanosine on ^{3}H-noradrenaline release in the presence of atropine* (n = 4–4). * *Significant difference* ($P < 0.05$) *from S_2/S_1;* † *S_4/S_3 compared with S_3/S_2*

Drug	S_2/S_1	S_3/S_2 with atropine (no drug)	S_4/S_3 with atropine + drug	*P*†
Control	0.94 (0.02)	1.05 (0.04)*	0.96 (0.02)	ns
Laudanosine 10 μmol litre^{-1}	0.97 (0.08)	1.03 (0.02)*	2.31 (0.09)	< 0.05
Atracurium 10 μmol litre^{-1}	0.94 (0.02)	1.05 (0.04)*	1.11 (0.04)	ns

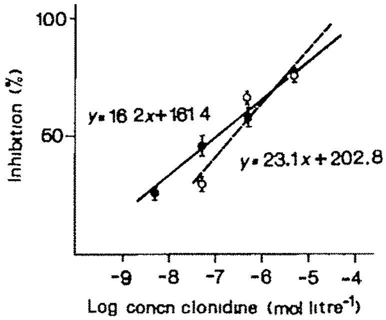

FIG. 3. Effect of clonidine on release of ^{3}H-noradrenaline evoked by stimulation (2 Hz, 240 stimuli) of the isolated right atrium of guineapig heart in the absence (●) and presence (○) of laudanosine 10 μmol litre^{-1}.

At low temperature, the production of laudanosine from atracurium is inhibited, therefore the possible antimuscarinic effects of atracurium were studied by keeping atracurium at 4 °C until immediately before use. Atracurium thus kept completely reversed the inhibitory effect of oxotremorine on ^{3}H-NA release (table II), but did not enhance the release of ^{3}H-NA above control values, as it did when added to the perfusion fluid and kept at 37 °C (table I, fig. 2).

In addition, the effects of atracurium and laudanosine were studied in the presence of atropine,—that is, when the presynaptic muscarinic receptors were already antagonized. In this case atracurium did not enhance ^{3}H-NA release. However, laudanosine induced ^{3}H-NA release (table III) to the same extent as when the muscarinic receptors were not inhibited.

Effect on histamine receptors. As atracurium has been reported [21] to release histamine, the effect of histamine on ^{3}H-NA release from guineapig atrium was investigated. Histamine 0.1 and 1.0 μmol litre^{-1} did not increase ^{3}H-NA release. The S_3/S_2 ratios were 0.98 (0.02) and 0.99 (0.03), respectively ($n = 3$–3). Also, the effect of atracurium 10 μmol litre^{-1} on release of hydrogen-3 was not affected by addition of either an H_1-receptor blocker (pyrilamine) or an H_2-blocker (cimetidine) (data not shown).

Involvement of laudanosine in the effect of atracurium

When atracurium was preincubated for 30 min at 4 °C there was no detectable laudanosine in the Krebs' solution and atracurium was not effective in enhancing release of noradrenaline in response to electrical stimulation. Laudanosine preincubated at 4 °C for 30 min was as effective as at

TABLE IV. *Atracurium and laudanosine kept in Krebs' solution at 4 °C or 37 °C for 30 min: effect on ^{3}H-noradrenaline release (expressed as ratio S_3/S_2) evoked by stimulation* (n = 4–4). ** Significant difference* (P < 0.05) *from control; † S_3/S_2 compared with S_2/S_1*

	Kept at 4 °C		Kept at 37 °C		
Drug	S_3/S_2	Laudanosine concn (μmol litre^{-1})	S_3/S_2	Laudanosine concn (μmol litre^{-1})	*P*†
Control	0.97 (0.03)		0.96 (0.04)		
Atracurium 10 μmol litre^{-1}	1.03 (0.02)	< 0.1	1.86 (0.12)	6.2 (1.1)	< 0.01
Laudanosine 10 μmol litre^{-1}	1.92 (0.52)*		2.10 (0.08)*		< 0.02

37 °C. When atracurium dissolved in Krebs' solution was kept at 37 °C, it enhanced release: the S_3/S_2 ratio increased from 0.96 (0.04) to 1.86 (0.12) and laudanosine 6.2 (1.1) μmol litre^{-1} was present in the Krebs' solution (table IV).

The release of noradrenaline is modulated by negative feedback via presynaptic alpha-2 adrenoceptors when noradrenaline is released into the synaptic cleft [22, 23]. Consequently, alpha-2 adrenoceptor blocking drugs enhance the release of noradrenaline in response to stimulation. Figure 3 shows that laudanosine did not affect the inhibitory effect of clonidine on ^{3}H-NA release. In addition, laudanosine 1–50 μmol litre^{-1} failed to prevent the effect of xylazine in blocking stimulation evoked (0.1 Hz) contractions of rat vas deferens (data not shown). These findings indicate that laudanosine has no alpha-2 adrenoceptor blocking activity.

DISCUSSION

Atracurium breaks down through Hofmann elimination to form laudanosine and a related quaternary acid, neither of which have neuromuscular blocking effects [24–26]. It has been suggested [2] that laudanosine may produce convulsions and central stimulation in animals [2, 8–11, 27]. In addition, jerky movements of the limbs were observed following administration of atracurium 0.6 mg kg^{-1} to patients with renal failure [28] under conditions in which higher plasma concentration of laudanosine can be expected [29, 30]. Basta and colleagues [7] found a small, but significant increase in heart rate and hypotension with doses of atracurium in excess of 0.4 mg kg^{-1}, but Lanier, Sharbrough and Michenfelder [31] failed to observe potentiation of lignocaine seizure threshold in cats following administration of atracurium.

We studied the effect of atracurium and laudanosine on chemical neurotransmission. The isolated right atrium of the guineapig was selected because release of noradrenaline can be studied easily [12, 32]. In addition, significant correlation had been found between noradrenaline-releasing action of drugs with antimuscarinic activity in *in vitro* experiments on isolated right atria, and tachycardia observed in patients in response to these drugs [12, 13, 20].

Both atracurium and laudanosine significantly enhanced the evoked release of ^{3}H-NA from isolated right atrium, but failed to affect release at rest. Atracurium enhanced the evoked release of noradrenaline well above the control value and antagonized the inhibitory effect of muscarinic receptor stimulation produced by oxotremorine on release of noradrenaline. When atracurium was kept at 4 °C until the tissue was perfused, there was no detectable laudanosine (table IV) in the bathing Krebs' solution. Under this condition atracurium still antagonized the inhibitory effect of oxotremorine on release of noradrenaline. However, when present, laudanosine did not influence the effect of oxotremorine. Therefore, it is likely that atracurium *per se* possesses antimuscarinic activity, but laudanosine does not. This action of atracurium is shared by other neuromuscular blocking drugs (gallamine and pancuronium) [12].

Laudanosine enhanced the evoked release of noradrenaline. Therefore, it seems likely that the several-fold increase in release of ^{3}H-NA observed in our studies following perfusion of high concentrations of atracurium was caused by laudanosine, although involvement of other metabolites cannot be excluded. This suggestion is supported by the finding that, when atracurium was kept at 4 °C (that is, when the Hofmann elimination was prevented), atracurium did not increase the release of noradrenaline. Our data indicate that the action of laudanosine is not mediated via antimuscarinic or alpha-2 adrenoceptor blocking activity mechanisms known to be able to enhance release of noradrenaline [22, 23].

Our investigation of the possible involvement of histamine in the noradrenaline-releasing activity of atracurium indicated that it is unlikely.

Atracurium is suitable for administration by infusion in patients during prolonged surgery or in intensive care units [33]. Plasma concentrations of laudanosine 0.2 $\mu g\ ml^{-1}$ (0.7 $\mu mol\ litre^{-1}$) [29, 30] and 1.9–5.1 $\mu g\ ml^{-1}$ (7–18 $\mu mol\ litre^{-1}$) [33, 34] were found in patients after administration of atracurium. The plasma concentrations of laudanosine found during surgical anaesthesia (0.7 $\mu mol\ litre^{-1}$) were less than those used in this study, whereas those reported during prolonged administration in the ICU were within the range (7–18 $\mu mol\ litre^{-1}$) that increased release of noradrenaline.

In summary, it has been shown [35, 36] that non-depolarizing neuromuscular blocking drugs such as tubocurarine and pancuronium possess presynaptic antinicotinic effects at the neuromuscular junction and thereby reduce the release of acetylcholine from motor nerve terminals. Pancuronium [12, 13] and gallamine [12, 20] enhance the release of noradrenaline from the atrial sympathetic nerve via inhibition of presynaptic muscarinic receptors. We have shown that atracurium has a presynaptic antimuscarinic activity, which is most probably clinically unimportant. Its metabolite, laudanosine, does not possess such an action, but does exhibit a strong noradrenaline-releasing action. This effect should be remembered when atracurium is used for prolonged administration in the ICU, particularly in patients with renal failure, in whom greater plasma concentrations of laudanosine may be expected [30, 37].

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EFFECT OF PROPOFOL ON THE MALIGNANT HYPERTHERMIA SUSCEPTIBLE PIG MODEL

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SUMMARY

Anaesthetic techniques for malignant hyperthermia susceptible (MHS) patients should include drugs which do not trigger MH and provide stress free conditions. Thus all new drugs should be screened for their susceptibility to trigger MH. We have screened propofol, using the MHS pig model. In none of the animals exposed to propofol, were there signs of MH, even after challenge with suxamethonium. However, the same animals developed MH when exposed to halothane alone or with suxamethonium Despite the problems of extrapolating from this study to man, it is unlikely that propofol may trigger an episode of MH.

Anaesthetic induced malignant hyperthermia (MH) in man is a severe and life-threatening event; thus all new anaesthetic agents should be screened for their susceptibility to trigger MH. We have used the MHS pig model to investigate the triggering capacity of propofol to induce MH.

METHODS

We studied 11 Pietrain pigs (weight 27 (SD 10) kg) chosen for their susceptibility to malignant hyperthermia. They were premedicated with droperidol 20 mg and atropine 0.25 mg i.m. Anaesthesia was induced 3 h later with i.v. propofol. The trachea was intubated and the lungs ventilated using a Monnal ventilator, with $F\mathrm{I}_{\mathrm{O}_2} = 1$. End-tidal carbon dioxide concentration ($\mathrm{E}'_{\mathrm{CO}_2}$) was maintained at approximately 4% using a capnograph. Suxamethonium 2 mg kg^{-1} was given i.v. after 30 min of propofol infusion. Susceptibility of the animal to MH was tested by the administration of 1% halothane, after discontinuing the propofol infusion. The infusion of propofol lasted 2–3 h. The diagnosis of MH was made on the basis of a persistent increased $\mathrm{E}'_{\mathrm{CO}_2}$ with constant ventilation, as the most sensitive marker of the syndrome [1, 2]. If hypercapnia failed to occur after 30 min exposure to halothane, suxamethonium 2 mg kg^{-1} i.v. was again administered. The following variables were monitored continuously: heart rate (HR) by means of an ECG; systemic arterial pressure (AP) by means of a femoral artery catheter which also allowed sampling for arterial blood-gas and biochemical analysis; cardiac output (CO) and mixed venous blood saturation ($S\bar{\mathrm{v}}_{\mathrm{O}_2}$) were determined by means of a Swan–Ganz catheter inserted via the internal jugular vein. $\mathrm{E}'_{\mathrm{CO}_2}$ was monitored continuously using a capnograph. Rectal and pulmonary arterial temperature were recorded continuously. Expired minute volume was measured by spirometry. We also measured stroke volume (SV), arterial blood saturation ($S\mathrm{a}_{\mathrm{O}_2}$), arterial pH and serum concentrations of potassium and calcium.

We calculated $\dot{V}\mathrm{CO}_2$ by means of the formula: $\dot{V}\mathrm{CO}_2 = \dot{V}\mathrm{E} \times \sqrt{F\mathrm{E}_{\mathrm{CO}_2}}$. Oxygen consumption ($\dot{V}\mathrm{O}_2$) was calculated: $\dot{V}\mathrm{O}_2 = (C\mathrm{a}_{\mathrm{O}_2} - C\bar{\mathrm{v}}_{\mathrm{O}_2}) \times \mathrm{CO}$.

Data were analysed using Student's *t* test for paired values.

RESULTS

The mean (SD) induction dose of propofol was 4.14 (1.54) mg kg^{-1}. Induction was smooth and permitted satisfactory tracheal intubation. The total maintenance dose of propofol was 48.4 (10.4) mg kg^{-1} for a duration of 2.9 (0.45) h (17.58 (7) mg kg^{-1} h^{-1}). In none of the animals was there any evidence of a malignant hyperthermia syndrome.

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TABLE I. *Variables measured during the experiment (mean (SD)). Values obtained after injection of suxamethonium during infusion of propofol and at the end of propofol compared with the results at induction or maintenance, and values obtained during MH compared with those at the end of propofol.* *$P < 0.05$; **$P < 0.01$

	Induction	Maintenance	Suxamethonium	End of propofol infusion	MH 5 min
HR (beat min^{-1})	136 (33) ($n = 11$)	137 (31) ($n = 11$)	133 (42) ($n = 5$)	121 (24) ($n = 11$)	149 (27)* ($n = 11$)
MAP (mm Hg)	84.5 (15.8) ($n = 11$)	106.1 (26.3) ($n = 11$)	83.0 (29.5) ($n = 6$)	97.0 (32.3) ($n = 11$)	71.4 (14.4) ($n = 11$)
CO (litre min^{-1})		4.24 (1.32) ($n = 10$)	4.99 (1.42) ($n = 5$)	3.77 (1.1) ($n = 10$)	4.56 (2.5) ($n = 9$)
SV (ml)		25.5 (5.6) ($n = 10$)	32.6 (10.8) ($n = 4$)	31.1 (8.2) ($n = 10$)	32.2 (22.3) ($n = 9$)
E'_{CO_2} (%)	3.9 (0.9) ($n = 11$)	4.2 (0.9) ($n = 11$)	6.2 (1.3)** ($n = 6$)	4.2 (1.2) ($n = 11$)	7.2 (1.6)** ($n = 11$)
$\dot{V}O_2$ (ml min^{-1})		86 (35.6) ($n = 10$)	98.3 (8.7) ($n = 4$)	92.2 (32) ($n = 7$)	271.3 (128)** ($n = 10$)
$\dot{V}CO_2$ (ml min^{-1})	233 (94) ($n = 11$)	199 (116) ($n = 11$)	371 (134)* ($n = 6$)	240 (147) ($n = 11$)	408 (200)* ($n = 11$)
Sa_{O_2} (%)		98.8 (0.6) ($n = 11$)	99.3 (0.3) ($n = 4$)	99.3 (0.6) ($n = 7$)	99.2 (2.5) ($n = 11$)
$S\bar{v}_{O_2}$ (%)		80.3 (8.5) ($n = 11$)	74 (4.5) ($n = 5$)	73.7 (10.5) ($n = 7$)	39.1 (13)** ($n = 10$)
Temperature (°C)	37.3 (1.1) ($n = 11$)	37.0 (1.5) ($n = 11$)	37.1 (1.6) ($n = 6$)	36.7 (1.5) ($n = 11$)	37.9 (2.1) ($n = 11$)
pH		7.46 (0.06) ($n = 11$)	7.37 (0.06)* ($n = 4$)	7.45 (0.09) ($n = 6$)	6.98 (0.04)** ($n = 10$)
Bicarbonates (mmol litre^{-1})		29 (3.2) ($n = 11$)	29 (4.1) ($n = 4$)	31 (4.9) ($n = 5$)	21 (2.8)** ($n = 10$)
Potassium (mmol litre^{-1})		4.6 (0.7) ($n = 7$)	4.9 (0.4) ($n = 4$)	4.4 (0.14) ($n = 5$)	7.5 (2)* ($n = 9$)
Calcium (mg litre^{-1})		103.2 (12.5) ($n = 5$)		104.2 (5) ($n = 4$)	120.4 (11.3)* ($n = 7$)

None of the variables measured showed significant variation during maintenance of anaesthesia and at the end of the infusion of propofol (table I).

The first injection of suxamethonium produced fasciculations accompanied by a rapid increase in E'_{CO_2}, from 0 to 2.6% (mean 1.2 (SD 1.3)). This did not last for more than 2–5 min, and there was a rapid return to baseline values, without any change in ventilation. In none of the animals investigated was there any evidence of malignant hyperthermia (persistent increase in E'_{CO_2}, rigidity or hyperthermia).

All 11 pigs developed malignant hyperthermia syndrome, either after halothane alone (four pigs), or in association with suxamethonium (seven pigs). Five minutes after the onset of the change in E'_{CO_2}, the increase was 1.5–7.1% (mean 3.1 (SD 1.8))—a significant difference ($P < 0.05$) compared with the increase during infusion of propofol.

The variables changed in a manner typical of MH (table I): increase in heart-rate; three-fold increase in oxygen consumption; two-fold increase in production of carbon dioxide; decrease in arterial pH, bicarbonate and mixed venous saturation, accompanied by an increase in serum K^+ and Ca^{2+} concentrations. All these changes were significant. Cardiac output and stroke volume increased only slightly (ns). Mean arterial pressure decreased slightly (ns). Central temperature was only slightly increased at the onset of MH (ns), and muscular rigidity had not developed 5 min later. These changes are typical of MH [3].

DISCUSSION

The absence of clinical and biochemical signs of MH during deep and prolonged anaesthesia with propofol in 11 MH sensitive pigs indicated that the agent was not an MH trigger in this model.

The MHS pig model is a valid experimental means of screening new anaesthetic agents, but care is required in interpretation of the results, as considerable variations exist in the sensitivity of the MHS pig model. Injection of suxamethonium during the propofol infusion was necessary because halothane is not a constant trigger of MH in this strain of pig [4]. The association of suxamethonium and halothane always triggers a typical crisis [4]. The administration of suxamethonium produced fasciculations and a concomitant increase in production of carbon dioxide, as in MH. The increase in production of carbon dioxide was probably the result of fasciculations [5], as it was small in magnitude and transient compared with the increase that occurred after administration of suxamethonium during halothane inhalation.

Droperidol premedication was unlikely to protect against a possible triggering action of propofol because of the time elapsed between premedication and induction of anaesthesia. However, it is not possible to speculate if propofol also has a protective action against MH, as occurs with other anaesthetic agents such as barbiturates or tranquillizers [6, 7].

We have used propofol safely in four MHS patients undergoing general anaesthesia. Although it would appear from this study and our clinical experience that propofol may be recommended for the MHS patient, considerable experience with MHS patients is required before it can be confidently stated that propofol is safe for the MHS patient.

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EFFECT OF GENERAL ANAESTHESIA ON THE MAGNETIC RESONANCE IMAGING SIGNAL FROM THE BRAIN

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SUMMARY

Magnetic resonance images of the brain were obtained in 10 female patients before and 2–6 h after a standard general anaesthetic. The longitudinal magnetic relaxation times (T_1) showed a non-significant decrease, whereas the transverse magnetic relaxation times (T_2) increased in all scans, with significant increases in the pons and corpus callosum. This suggests that general anaesthesia may be associated with structural changes in the brain at a molecular level.

Medical magnetic resonance imaging (MRI) systems usually measure the activity of hydrogen nuclei (protons). As most body tissues are composed mainly of water, MRI is, in effect, a method of determining water content and changes in the distribution and molecular environment of water molecules in the body. The measurements used are T_1, the spin lattice relaxation time (or longitudinal magnetic relaxation time) and T_2, the spin-spin lattice relaxation time (or transverse magnetic relaxation time). T_1 is dependent on the interaction of protons with surrounding nuclei and molecules, that is, the lattice. T_2 depends on the interaction of protons with one another. Areas in the body with low water content have short T_1 values, whereas areas with high water content have long T_1 values.

Mander and colleagues [1] found a significant increase in T_1 in patients immediately after electroconvulsive therapy (ECT). However, five volunteers in the study who received the same anaesthetic but without ECT showed non-significant decreases in T_1. This raised the possibility that general anaesthesia may itself alter the MRI signal from the brain. The present study has explored this possibility.

METHODS AND RESULTS

We studied 10 women (ASA I or II, aged 26–50 yr (mean 39.9 yr)) scheduled for cone biopsy of the cervix, following an explanation of the procedure. All patients gave written consent to the study, which was approved by the local Ethics Committee. Patients receiving any medication other than the contraceptive pill, or with a history of epilepsy, were excluded.

Each patient had an MRI brain scan on the afternoon before surgery. Cone biopsy was carried out using a standard anaesthetic technique. Premedication with temazepam 20 mg by mouth was given 1 h before operation. Anaesthesia was induced with thiopentone 4–7 mg kg^{-1} i.v. and diamorphine 2.5 mg i.v., and maintained with nitrous oxide, oxygen and enflurane administered via a facemask and a circle absorber system with 3 litre min^{-1} fresh gas flow. After anaesthesia, when the patients were recovered sufficiently, they underwent a second scan. This was carried out 2.5–6.5 h (mean 4.4 h) after induction of anaesthesia.

An M & D Technology Ltd 0.08 Tesla resistive magnetic resonance imaging system was used. For each patient T_1 and T_2 measurements were made on 12-mm thick transverse sections of the brain at a level 10 mm above the widest point of the lateral ventricles. T_1 and T_2 measurements were made also from sagittal sections in small areas of the pons, midbrain and corpus callosum. The T_1 and T_2 values of individual pixels are calculated automatically by the scanner's computer, but first the margins of the relevant brain areas have to be defined. This was done independently by two raters, using a manual cursor. The means of the

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TABLE I *Mean T_1 and T_2 values before and after anaesthesia. Differences assessed using Wilcoxon's rank test for matched pairs*

	Right transverse	Left transverse	Pons	Midbrain	Corpus callosum
T_1 (ms)					
Before	332.0	328.2	314.1	353.4	279.4
After	327.9	328.2	308.9	352.2	275.8
Mean change	−4.1	0	−5.2	−1.2	−3.6
	ns		ns	ns	ns
T_2 (ms)					
Before	103.2	101.9	92.0	98.2	87.0
After	105.0	103.2	96.5	99.4	97.0
Mean change	+1.8	+1.3	+4.5	+1.2	+10
	ns	ns	$P < 0.05$	ns	$P < 0.01$

two sets of relaxation times derived were used in all subsequent calculations. The significance of the mean changes in T_1 and T_2 values were assessed using Wilcoxon's rank test for matched pairs.

The mean T_1 value decreased after anaesthesia and surgery in the different sections examined, apart from the left transverse section, in which there was no change (table I). However, none of these changes was significant.

The mean T_2 increased in all sections measured, significantly in the pons and corpus callosum (table I).

COMMENT

The main difficulty in studying patients before and after anaesthesia and surgery is the delay caused by the patient's need to recover from the procedure before re-scanning. In Mander's study and another by Scott (unpublished observations) the subjects underwent ECT, which is one of the few procedures that can reasonably be undertaken in the MRI suite; the time taken before re-scanning was approximately 30 min. The mean time between induction of anaesthesia and re-scanning in this study was 4.4 h because, in addition to the need to allow the patient to recover, the MRI scanner was not always immediately available. It is possible, therefore, that the observed changes would have been greater had re-scanning taken place sooner.

T_1 values reflect the water content of different tissues [2] and changes in T_1 may reflect shifts in the distribution of water molecules within the brain. The ECT studies showed an increase in T_1, which may have been offset partially by the effect of the anaesthetic, as T_1 in the volunteers (anaesthesia alone) showed a small decrease. As ECT is known to produce a temporary breakdown of the blood–brain barrier [3], Mander and colleagues suggested that the increase in T_1 which they observed after ECT was caused by osmotic changes secondary to changes in the blood–brain barrier. The mean T_1 values decreased in four of the five brain areas examined, and in both cerebral hemispheres in the five volunteers, although none was significant ($P < 0.05$). These changes accord with the findings in the present study, so it may be that a genuine change is occurring and that, with larger numbers of patients, a statistically significant change would be obtained. Although the precise cause of this change is unclear, it probably indicates an alteration in either the density or the molecular environment of water molecules in the tissue. Mander's group [4] showed that ingestion of 14 units of alcohol (half a bottle of spirits) by normal volunteers was associated with a significant decrease in T_1 in several parts of the brain, consistent with the observation that alcohol promotes diuresis and dehydration. As alcohol resembles general anaesthetic agents in many pharmacological aspects, including lipid solubility, the mechanism involved may be the same.

The cause of the increase in T_2 (which was significant), which was not measured in the earlier study by Mander and co-workers [4] also cannot be explained at present. We believe that this is the first study in human subjects of changes in T_2 associated with anaesthesia. Animal studies have been concerned largely with the effect of experimental physiological insults [5], or with the uptake and elimination of anaesthetic agents, using a variety of different resonating nuclei (for example phosphorus-31, carbon-13, fluorine-19 and sodium-23, in addition to hydrogen-1) [6]. Reid (unpublished observations) has also confirmed the findings of Mander's group that electrically induced convulsions in rats produce a temporary increase in T_1, but he did not measure changes in T_2. We suggest that the changes may result from structural alterations which have taken place at a molecular level, and this study describes the changes found using one method of anaesthesia. It seems clear, however, that the phenomenon merits further investigation with other anaesthetic agents and, in particular, study of the time course of the changes produced.

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ACCELERATED RECOVERY FROM COMBINED ATRACURIUM–VECURONIUM NEUROMUSCULAR BLOCK

J. A. STIRT

SUMMARY

Patients given combinations of non-depolarizing neuromuscular blocking drugs have been reported to recover from neuromuscular block more rapidly than patients given a single drug. This study was designed to assess if this phenomenon occurred with the combination of atracurium and vecuronium. During nitrous oxide–fentanyl anaesthesia, 30 adult patients were allocated randomly to receive atracurium 0.5 mg kg^{-1}, vecuronium 0.1 mg kg^{-1}, or a combination of atracurium 0.125 mg kg^{-1} + vecuronium 0.025 mg kg^{-1}. All patients had 100% neuromuscular block, and times to block onset did not differ significantly between the three groups. Recovery to 10, 25, 50 and 90% of control twitch height was significantly faster in the group receiving the combination of drugs.

It was observed fortuitously that relatively small doses of atracurium in combination with vecuronium seemed to produce complete neuromuscular block, with a distinctly more rapid recovery of muscle twitch, than when a single, larger intubating dose of each relaxant alone was used.

Combinations of non-depolarizing neuromuscular blockers have been used in numerous clinical studies in man [1–5]. Two previous reports have demonstrated more rapid recovery from the same degree of block in patients given potentiating combinations of blockers (pancuronium–dimethyltubocurarine [3] or pancuronium–tubocurarine [4]) than those given a single agent.

A prospective investigation of the combined use of atracurium and vecuronium was performed to study and quantify this phenomenon in more detail.

METHODS AND RESULTS

The study was approved by the institution's Human Investigation Committee, and written informed consent was obtained from all patients. We studied 30 adult patients, ASA physical status I or II. No premedication was given. After application of an arterial pressure cuff and electrocardiographic electrodes, anaesthesia was induced with thiopentone 4–6 mg kg^{-1} i.v. and maintained with fentanyl 3–5 μg kg^{-1} i.v. and 67% nitrous oxide in oxygen.

Neuromuscular block was monitored using a chart recorder and a force transducer (Grass FT-10) which measured adductor pollicus twitch tension in response to supramaximal ulnar nerve stimulation at 0.15 Hz delivered for a duration of 0.15 ms via 25-gauge needles placed subcutaneously.

Patients were allocated randomly to receive atracurium 0.5 mg kg^{-1} (4 × ED_{90}), vecuronium 0.1 mg kg^{-1} (4 × ED_{90}), or atracurium 0.125 mg kg^{-1} (ED_{90}) followed immediately by vecuronium 0.025 mg kg^{-1} (ED_{90}). We measured the times to initial twitch depression and to maximum twitch depression, the magnitude of neuromuscular block produced and the times to 10, 25, 50, 75 and 90% recovery of initial twitch height.

Statistical analysis was performed using one-way analysis of variance (ANOVA); groups which differed significantly by ANOVA were tested with two-tailed t tests (Bonferroni correction) to determine differences between groups. $P < 0.05$ was considered significant.

Mean ages and weights did not differ significantly between the three groups. All patients had 100% neuromuscular block (table I). Times to

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TABLE I. *Neuromuscular block and recovery (mean (SEM)) following atracurium 0.5 mg kg*$^{-1}$*, vecuronium 0.1 mg kg*$^{-1}$*, or atracurium 0.125 mg kg*$^{-1}$*+vecuronium 0.025 mg kg*$^{-1}$ *Significant differences* ($P < 0.05$) *compared with. *atracurium 0.5 mg kg*$^{-1}$ *and vecuronium 0.1 mg kg*$^{-1}$ *groups; †atracurium 0.5 mg kg*$^{-1}$ *group*

Group	Time to initial twitch height depression (min)	Time to maximum neuromuscular block (min)	Time to % recovery from neuromuscular block (min)				
			10%	25%	50%	75%	90%
Atracurium 0.5 mg kg^{-1} ($n = 10$)	1.0 (0.2)	3.0 (0.4)	42 (2)	48 (2)	54 (2)	60 (2)	66 (2)
Vecuronium 0.1 mg kg^{-1} ($n = 10$)	1.0 (0.2)	3.0 (0.3)	38 (2)	43 (2)	50 (3)	58 (4)	66 (4)
Atracurium 0.125 mg kg^{-1} + vecuronium 0.025 mg kg^{-1} ($n = 10$)	1.4 (0.1)	4.2 (0.4)	27 (1)*	32 (1)*	38 (2)*	43 (2)†	48 (2)*

initial and maximal twitch height depression did not differ significantly between the groups (table I).

Profiles of twitch height recovery are also shown in table I. Recovery to 10, 25, 50 and 90% of control twitch height was significantly faster in the group receiving the atracurium–vecuronium combination than in the other two groups.

COMMENT

Two previous studies [3, 4] using single bolus doses of combinations of non-depolarizing neuromuscular blocking drugs in man demonstrated no significant differences in onset time or maximum block between groups receiving single or combined relaxant drugs. Time to 25% recovery of twitch height was significantly shorter in groups receiving combinations than in those receiving a single agent [3, 4].

We have studied the combination of atracurium and vecuronium. Although not significantly different, the slightly longer times to initial and maximal twitch height depression in the group receiving the combination of drugs, together with the significantly shorter recovery times in this group, may indicate that the drug combination was less potent than the doses in the single agent groups. This is not surprising, as only 25% of each of the single relaxant doses was used in the combination group.

The doses of drugs were selected to simulate clinical use. Atracurium 0.5 mg kg^{-1} and vecuronium 0.1 mg kg^{-1} are doses used commonly for tracheal intubation in man. Spontaneous recovery from these doses to 25% of control twitch height has been reported to occur in approximately 40 min, and 90% recovery in approximately 55 min [6]. The results of our study are consistent with these values.

Twitch tension recovered significantly faster after complete neuromuscular block in the group receiving combined atracurium and vecuronium (table I). Thus neuromuscular block in patients receiving a combined atracurium–vecuronium regimen (2 × ED_{90} equivalent) was potentially readily reversible (spontaneous recovery to 10% of control twitch height) 10–15 min before that in patients receiving an intubating dose of either atracurium or vecuronium alone (4 × ED_{90}). Similarly, spontaneous recovery to 90% of control twitch height occurred almost 20 min faster (approximately 33% more rapidly) in the group receiving the drug combination than in either group receiving one agent.

The shorter recovery time produced by a combination of atracurium and vecuronium may be useful in situations where a brief period of intense relaxation is required; use of the doses administered to the combined atracurium–vecuronium group (2 × ED_{90} equivalent) may produce conditions suitable for intubation in several minutes. This regimen would not be suitable for rapid sequence intubation, although more rapid onset might be obtained by increasing the combined doses.

What other advantages might be offered by the use of a combination of atracurium and vecuronium in the doses used in this study? First, use of the combination of neuromuscular blockers would decrease the expense of producing conditions suitable for intubation, and avoid the use of suxamethonium. In addition, the more rapid recovery might, in some instances, allow for use of smaller than usual doses of relaxant antagonists, and occasionally obviate the need for their use. Faster recovery may also reduce the frequency of unsuccessful antagonism of neuromuscular block. Finally, the incidence of cardiovascular systemic side effects produced by atracurium may be diminished by the use of the combined regimen described.

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CORRESPONDENCE

THE ANAESTHETIST'S ACTIVITIES IN THE OPERATING THEATRE

Sir,—Drs McDonald and Dzwonczyk made some interesting observations and raised some pertinent points for discussion in their study of the activity of anaesthetists in the operating theatre [1], but they have come, by faulty logic, to the wrong conclusions.

Freeing another 55% of intraoperative time would not necessarily make anaesthesia safer. That conclusion could be drawn only from a study showing that anaesthetists, relieved of these activities, made fewer errors that led to harm. There is no need for the anaesthetist to be observing the patient continuously, provided that the patient is observed often enough, and that the anaesthetist is capable of detecting an error before it has become a danger.

Similarly, showing that anaesthetists spend 12% of their time filling in the record does not permit the conclusion that this task should be automated. Even less does it permit the conclusion that complex "intelligent" monitors are needed. There is great appeal in trying to "automate human error out of the system" [2], but increasing automation can bring its own problems. The authors can suggest that these techniques should be investigated, but they have no grounds for suggesting a need.

The authors failed to comment on the consequences of their recommendations. One cannot make pronouncements on a need for extra personnel and complicated equipment without commenting on the cost. Cost must always be balanced against return, and it must be realized that, whatever is done and however much is spent, humans will always make errors [3].

The authors' final comment, that it is "noteworthy" that the technology for sophisticated integrated systems is available, is the last reason to apply it without evaluation. Technology has a momentum of its own, and we must be wary of feeling that we must use it just because it is there. In a recent editorial in *Anesthesiology* [4], on the subject of the automatic delivery of anaesthetic agents, Brater wrote: "... I know of no method sufficiently accurate and universal that it can serve as a substitute for clinical judgement. ... although I enthusiastically endorse the directions pursued in this study, I am adamant that they should be implemented only by those skilled in their use who have appropriate concern about their limitations." This is a wise philosophy.

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Sir,—We appreciate Goodman's comments and applaud his insistence on clinical judgement as a prerequisite for safe practice. It is correct to say that our study does not show that reducing interference from non-critical tasks will assure safe anaesthesia; we doubt such a study would be feasible. Isolating the effect of individual changes on medical progress (especially such broadly construed notions as "workload" on variables such as "error rate") is extraordinarily difficult and may be impossible in the multivariate and rapidly changing world of the 1990s

We agree with Dr Goodman that additional time spent monitoring the patient does not, itself, guarantee safer anaesthesia. The role of the anaesthetist is to use the additional intraoperative time to acquire and use information on the physiological state of the patient in order to improve his/her clinical judgement. We suggested means to reduce the complexity of anaesthetist behaviour, thereby increasing anaesthetist vigilance [1]. In this way, the patient would receive the maximum benefit from the anaesthetist's training and experience.

The automatic record keepers presently available in the United States could be used beneficially in the operating theatre, but are not "intelligent" monitors or replacements for the anaesthetist. On the contrary, these machines merely perform a repetitive clerical task which we and others [2] have shown consumes approximately 10–15% of intraoperative time. We recommend using technology, not in an effort to "automate human error out of the system" [3], but more "to keep the operator in the loop, perhaps doing so by employing enhanced information and decision support systems" [4].

Analysis of monitoring costs [5] suggests that automatic record keeping may already be economically attractive. Twelve percent of intraoperative time is a relatively large fraction to spend performing a primarily clerical task. This time would be spent better in observing the patient and giving the anaesthetic.

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BOOK REVIEWS

Imaging and Labelling Techniques in the Critically Ill. Edited by W. Kox, J. Boultbee and R. Donaldson. Published by Springer-Verlag. Pp. 188; indexed; illustrated Price £93.00

In the preface, the Editors state that their objectives are to introduce the reader to developments in diagnostic and therapeutic imaging techniques applicable to the patient undergoing intensive care The techniques outlined include standard chest radiography and much more sophisticated methods. This is a multi-author book and there are differences in presentation and style, but it is well produced and a pleasure to handle.

It is divided logically into five sections, each of which contains three or four sub-divisions. The sections are: the brain and central nervous system, the lung, the cardiovascular system and the abdomen The final section is devoted to special techniques and recent advances.

Sufficient information is given in each sub-section to enable the intensive therapy unit specialist to appreciate what techniques are available for the patients under his care. A number of the contributors emphasize that some of these techniques are not truly applicable to the patient in the I T.U. unless they can be transported to the Radiology Department relatively unencumbered with tubes, i.v. infusions, etc. Often this is not a problem, but there are circumstances in which patients cannot be moved and therefore some of the new techniques are of great interest but are of limited value. For example, magnetic resonance imaging is discussed by two contributors. Access to the patient undergoing this technique is a major difficulty, and there are restrictions on the use of metal objects both on the patient (particularly cardiac pacemakers) and within several feet of him. These disadvantages are well recognized by the contributors.

At the other end of the scale, there is a chapter on standard chest radiography. This should be most useful but, unfortunately, many of the x-rays are reproductions of portable films, which limits their usefulness The reviewer is also tempted to take issue with some of the diagnostic labels attached

Chapter 4 conveys the impression of a paper intended for submission to a scientific journal. The authors describe the measurement of jugular venous bulb oxygen saturation and cerebral blood flow measurement.

Chapter 6 describes the use of computed tomography in acute respiratory failure. In addition to outlining the possible value of the method to demonstrate topographical distribution of pulmonary pathology (including pneumothorax), an attempt is made to quantitate lung densities. This is interesting, but insufficient data are given to allow the reader to evaluate the method and, essentially, it is a first report of work in progress Again, the quality of the illustrations is poor.

This is followed by one of the most useful sections in the book, which describes radionucleide imaging of the lung. It is comprehensive and clear and the benefits of the method are enumerated. Unfortunately, the contributor has not been served well by the publisher, because the illustrations to the chapter are displaced from the text citations.

There is an exemplary introduction to the use of cardiac ultrasound which appears, in less than 1500 words, to be totally self explanatory. The book ends with an introduction to future developments; there is a beautifully illustrated section on the use of radio-labelled blood cells in the investigation of the critically ill patient.

There is a list of useful references at the end of each section, and the index is helpful.

The reviewer feels that the editors have achieved much of what they have intended. Some shortcomings result mostly from the quality, labelling and placing of the many illustrations. In some sections the illustrations are self explanatory, but in others there are no arrows or diagrammatic outlines of the reproduced photographs to help the uninitiated. Their usefulness is marred by the assumption that the reader may interpret body compartments and cavities without instruction As the cost (£93.00 for 188 pages) presumably reflects the number and complexity of the illustrations, the reviewer does not believe that this book represents a wise purchase for an individual clinician who requires an introduction to the subject.

J. C. Stoddart

Pocket Manual of Anesthesia, 1st Edn. Edited by G Lenz, B. Kottler, R. Schorer and W. E. Spoerel. Published by B. C Decker, Inc, Birmingham, Ontario. Pp 318; indexed illustrated Price £14

All anaesthetists have occasion to require a convenient source of vital information, either as an *aide-memoire* when memory fails, or to relearn the dose in $\mu g\ kg^{-1}\ min^{-1}$ of an infrequently used drug. The examination candidate may also seek a source of condensed information and be tempted to obtain a copy of the *Pocket Manual of Anesthesia*. Published originally in German, the book has been translated and adapted by Professor W. E. Spoerel of The University of Western Ontario

The preface to the German Edition implies that its purpose is to provide relevant facts and data in a pocket sized package for use in theatre. Although it is of an appropriate size, and contains a wealth of useful information, it has several irritating and perhaps misleading faults which detract from a book for the U.K market

Non-S.I. units and American spelling are tolerable, and American drug names such as Lidocaine and Demerol are known widely, but this book goes further and quotes American drug dilutions (e.g succinylcholine 20 mg ml^{-1}), devotes a full two pages to Propafenon, a drug not available in the U.K , yet omits drugs used commonly in the U.K., such as alcuronium, diamorphine and ouabain It suggests three oral premedication regimens for paediatric use, two of which are not available in the U K

In addition, there are many serious omissions. In the section on diabetes, for example, there is no mention of potassium supplements in the description of perioperative insulin regimens.

Given that much useful information is contained in the text, it is a pity that the index does not indicate which page numbers are important. Five page numbers are given for malignant hyperpyrexia in the index, only one of which gives useful information on the condition. In the section entitled Suggested Reading, of the 57 references quoted, only 24 are in English!

It is unfortunate that what must be a useful handbook in German has not been adapted fully to the English language. Those intending to spend time in North America may find it useful but, at present, it can not be recommended for use in the U.K

B. Meiklejohn

Acupuncture Treatment and Anaesthesia, 4th Edn. Edited by M. Salim. Published by The Army Press, Rawalpindi, Pakistan. Pp. 686; indexed; illustrated. Price $15.

This book is the 4th edition of a text that appeared first in 1974. The author is a western-trained anaesthetist who currently practises medicine in Pakistan. In addition to his basic medical skills, Dr Salim has developed over many years an intense interest in the management of pain and, in particular, the application of acupuncture to the relief of both acute and intractable pain.

This text comprises a series of monographs on the theory, practice and treatment of disease through acupuncture, and includes contributions from a number of internationally famous authors. The early part is devoted to the history of acupuncture and its gradual evolution as part of western practice. The information is concise and key references have been provided to substantiate the physiological and scientific basis of acupuncture.

In the second section, the practical aspects of acupuncture therapy are described. Information is provided on such issues as needling techniques, position of patients, complications and contraindications. There follows a large section, approximately 30% of the text, which covers descriptions of the various channels, the theories of Yin and Yang and the various modes of acupuncture such as hand, foot and ear treatment. The information is displayed clearly, but is no different from that found in any standard text on acupuncture medicine, although the author has attempted to provide references and explanations where appropriate. Practical information is provided on the selection of acupuncture points, but the subject matter is wide ranging and includes chapters on such varied issues as obesity, psoriasis, impotence and the maintenance of skin beauty, in addition to the more common musculoskeletal disorders.

In the final section of this book, Pain and Anaesthesia, the author tries to discuss a number of related issues concerning pain theory and management. There is a strong influence from the multiple authorship and, whilst the majority of statements are factually correct, the articles lack depth and originality. Clearly an attempt has been made to discuss every aspect of pain therapy, but insufficient space has been devoted to individual subjects, with the result that several chapters appear elementary.

In conclusion, I feel that this book is a good introductory text for those wishing to gain a little insight into acupuncture and its relationship to pain management, but would certainly not stimulate those with any experience in treating pain.

P. J. D. Evans

Clinical Anatomy for Anesthesiologists Edited by R. S. Snell and J. Katz. Published by Appleton & Lange, California. Pp. 328; indexed; illustrated. Price £77.00.

This book is the fruit of collaboration between Dr Katz, Professor of Anesthesiology in San Diego and Dr Snell, Professor of Anatomy in Washington and an author of several well-known texts on anatomy for medical students Thus many of the illustrations and diagrams have been taken from four texts written by Dr Snell specifically for medical students.

This book is written "to provide the anesthesiologist with a basic knowledge of anatomy necessary for practising anesthesiology" It therefore comprises sections on the respiratory, cardiovascular, nervous and autonomic nervous systems. It is illustrated liberally with figures, x-rays and photomicrographs, many of which are in colour. Each chapter is accompanied by a list of clinical problems, followed by answers to these problems. The majority of these are suitable for an undergraduate, but would be elementary or inappropriate for the anaesthetist. The final chapter on perception of pain and control of muscular activity describes in some detail the classical pain pathways with a clear account of the gate control theory, but omits discussion of opioid receptors and their localization in the CNS.

The section on neurophysiology is comprehensive. Attempts are made to render the chapter on "Nerve fibres and spinal nerves" relevant to the anaesthetist by accounts of local anaesthetic nerve blocks. However, these accounts are devoid of vital practical information which makes the text quite unsuitable as a primer of regional anaesthesia. For example, the ulnar nerve is described as passing between the olecranon process of the ulna and medial epicondyle of the humerus where it may be palpated and infiltrated with a local anaesthetic agent. Textbooks of regional anaesthesia suggest that blocks should not be performed at this site because of the risk of neuritis and that a higher level in the upper arm should be chosen. Details of anaesthetic agents and volumes are not included.

This book cannot be recommended. Whilst it contains excellent and well illustrated accounts of anatomy most relevant to the anaesthetist, the same information is freely available in many standard textbooks of anatomy for a fraction of the cost. Such clinical information as it contains varies from being too elementary for the postgraduate, inappropriate for the anaesthetist, or too inadequate to use for guidance in the practical performance of nerve blocks or other practical procedures.

G Smith

AUTHOR INDEX

VOLUME 62, 1989

British Journal of Anaesthesia

ARS = Anaesthetic Research Society papers
C = Correspondence
E = Editorial
R = Book review

Ackers, J. W. L. *see* Evans, R. D. 243–247
Adnet, P. *see* Krivosic-Horber, R. 691–693
Agoston, S. *see* Khuenl-Brady, K. S., (*ARS*) 225–226P; Wierda, J. M. K. H. 194–198
Aguilar Sanchez, J. L. *see* Montero Matamala, A. 637–640
Ainsworth, Q. P. and Howells, T. H. Transilluminated tracheal intubation 494–497
Aitkenhead, A. R. *see* Worsley, M. H., (*C*) 114
Ali, H. H. *see* Dresner, D. L. 331–334
Alifimoff, J. K. *see* Goudsouzian, N. G. 263–268
Andersen, P. E. *see* Christensen, P. A. 258–262
Anderson, S. J. *see* Loughnan, B. A., (*ARS*) 223P
Anderton, J. M., Keen, R. I. and Neave, R. *Positioning the Surgical Patient*, (*R*) 238
Andreasen, F. *see* Schurizek, B. A. 129–137; 674–682
Andrews, E. B. *see* Jick, H. 590–595; Lawson, D. H. 596–600
Ayres, S. M., Schlichtig, R. and Sterling, M. J., (editors) *Care of the Critically Ill*, 3rd Edn, (*R*) 117

Bagshaw, R. J. Hypotensive agents: an animal model, (*C*) 112
Baker, D. J. *see* Turner, G. A. 279–286
Baker, R. D. *see* Meakin, G. 655–658
Banssillon, V. *see* Chassard, D. 522–526
Baraka, A., Louis, F., Noueihid, R., Diab, M., Dabbous, A. and Sibai, A. Awareness following different techniques of general anaesthesia for Caesarean section 645–648
Barker, M. *see* Cook, P. R. 402–408
Barnes, P. K. *see* Millar, S. W. 153–158; Tyler, C. K. G. 462–466
Baskett, P. and Weller, R., (editors) *Medicine for Disasters*, 1st Edn, (*R*) 117–118
Beckett, G. J. *see* Ray, D. C 553–559
Becq, M. C. *see* Krivosic-Horber, R. 691–693
Bedford, R. F. *see* Shah, N. K 150–152
van Beem, H., Van Peer, A., Gasparini, R., Woestenborghs, R., Heykants, J., Noorduin, H., van Egmond, J. and Crul, J. Pharmacokinetics of alfentanil during and after a fixed rate infusion 610–615
Bell, P. F. and Mirakhur, R. K. Comparison of mechanomyography and integrated electromyography for monitoring suxamethonium block, (*ARS*) 225P
Bellhouse, C. P. and Doré, C. Predicting difficult intubation, (*C*) 469
Bencini, A. F. *see* Wierda, J. M. K. H. 194–198
Bendixen, D. *see* Hansen, M., (*C*) 237
Best, C. J., Ewart, M. and Sumner, E. Perioperative complications following the use of vancomycin in children: a report of two cases 576–577
Bigler, D. *see* Scott, N. B. 253–257
Biswas, C., Jana, N. and Maitra, S. Bilateral pneumothorax following tracheal intubation 338–339
Black, A. M. S. Effect of suxamethonium given during recovery from atracurium, (*C*) 348–349
Black, G. W. *see* Dwyer, R., (*ARS*) 219–220P; Sampaio, M. M. 199–201
Boaden, R. W. *see* Tackley, R. M. 46–53
Booij, L. H. D. J. *see* Scheepstra, G. L. 54–60; 92–94
Boston, V. *see* McCafferty, D. F 17–21
Bottiglieri, T. *see* Royston, B. D. 419–424
Boultbee, J. *see* Kox, W., (*R*) 701
Bowler, G. M. R. *see* Mitchell, R. W. D., (*C*) 113
Boyd, S. G. *see* Loughnan, B. A., (*ARS*) 223P
Boyer, A. *see* Wierda, J. M. K. H. 194–198
Branche, C. *see* Jick, H. 590–595; Lawson, D. H. 596–600
Brandom, B. W., Woelfel, S. K., Ryan Cook, D , Weber, S., Powers, D. M. and Weakly, J. N. Comparison of mivacurium and suxamethonium administered by bolus and infusion 488–493
Braude, N. and Ludgrove, T. Neurogenic pulmonary oedema precipitated by induction of anaesthesia 101–103
Brock-Utne, J. G., Rout, C., Moodley, J. and Mayat, N. Influence of preoperative gastric aspiration on the volume and pH of gastric contents in obstetric patients undergoing Caesarean section 397–401
Brockway, M. S., Murray, A. and Kenny, G. N C. Cardiovascular and respiratory effects of ketorolac and alfentanil during anaesthesia, (*ARS*) 224–225P
Brodsky, J. B. *see* Samuels, S. I. 216–218
Brown, D. T. *see* Pugh, G. C. 601–609
Bruce, W. C. and Soni, N. C. Preliminary evaluation of the Enclosed Magill Breathing System 144–149
Brugman, E. *see* Vangerven, M. 98–100
Brunner, J. X. and Wolff, G *Pulmonary Function Indices in Critical Care Patients*, 1st Edn, (*R*) 351
Bunemann, L. *see* Jensen, K. 321–323

Campbell, I. T., Willatt, D. J., Childs, D. and Stell, P. M. Arterial oxygenation after different types of major head and neck surgery, (*ARS*) 231–232P
Campbell, W. I. and Watters, C. H Venous sequelae following i.v administration of diclofenac 545–547
Canfell, P. C. *see* Khuenl-Brady, K. S., (*ARS*) 225–226P; Tateishi, A. 548–552
Canning, J., Elwell, A. and Ward, S. Comparison of the Elwell Neuromuscular Indicator and the Datex Relaxograph, (*ARS*) 226P
Capogna, G. *see* Celleno, D. 649–654
Carli, F., Ramachandra, V., Gandy, J., Ford, G. C., Merritt, H., Read, M. and Halliday, D. Whole body protein turnover during anaesthesia and surgery, (*ARS*) 220P

Carli, F. *see* Ramachandra, V 409–414

Carlisle, K. M. *see* Wolf, A. R., (*ARS*) 221–222P

Carrie, L. E. S. and Simpson, P. J. *Understanding Anaesthesia*, 2nd Edn, (*R*) 472

Casey, P. B. *see* Patterson, K. W., (*ARS*) 222–223P

Castagnoli, K. P. *see* Khunl-Brady, K. S , (*ARS*) 225–226P

Celleno, D., Capogna, G., Tomassetti, M., Costantino, P., Di Feo, G. and Nisini, R. Neurobehavioural effects of propofol on the neonate following elective Caesarean section 649–654

Cerra, F. B., (editor) *Perspectives in Critical Care Medicine*, (*R*) 583–584

Charters, P. *see* Fahy, L., (*ARS*) 234P; Horton, W. A. 6–12

Chassard, D., Joubaud, A., Colson, A., Guiraud, M., Dubreuil, C. and Banssillon, V Auditory evoked potentials during propofol anaesthesia in man 522–526

Childs, D. *see* Campbell, I. T., (*ARS*) 231–232P

Christensen, N. J. *see* Tønnesen, E. 327–330

Christensen, P. A., Noreng, M., Andersen, P. E. and Nielsen, J. W. Electroacupuncture and postoperative pain 258–262

Christian, A. S., Ellis, F. R. and Halsall, P. J Is there a relationship between masseteric muscle spasm and malignant hyperpyrexia? 540–544

Christys, A R., Moss, E. and Powell, D. Retrospective study of early postoperative convulsions after intracranial surgery with isoflurane or enflurane anaesthesia 624–627

Claffey, L. P., O'Toole, D. P., Schell, J., Tormey, W. and Cunningham, A. J Blood:CSF glycine concentration gradient following a controlled i.v. infusion in dogs, (*ARS*) 234–235P

Clarke, R. S. J. *see* Dwyer, R., (*ARS*) 219–220P

Coe, P. *see* Fairbrass, M. J. 66–69

Coenen, L. G. J. *see* Scheepstra, G. L. 54–60

Coetzee, A. and van der Merwe, W., (editors) *An Introduction to Anaesthesiology*, (*R*) 471

Cole, P. V. *see* Sury, M. R. J., (*C*) 112

Coley, S. Anaesthesia of the skin, (*E*) 4–5

Collier, P. S. *see* Flynn, R. J. 87–91

Colquhoun, A. D. *see* Reed, P. N 316–318

Colson, A. *see* Chassard, D. 522–526

Colvin, J. R. *see* Hodsman, N. B. A. 527–531

Conseiller, C. *see* Lirzin, J. D. 641–644

Cook, D. R. and Marcy, J. H., (editors) *Neonatal Anaesthesia*, 1st Edn, (*R*) 472–473

Cook, P. R., Myers, D., Barker, M. and Jones, J. G. Blood–brain barrier to pertechnetate following drug-induced hypotension 402–408

Cosaert, P *see* Vangerven, M. 98–100

Costantino, P. *see* Celleno, D. 649–654

Couri, D. *see* Hanna, A. N. 429–433

Coventry, D. M. and Todd, J. G Alkalinization of bupivacaine for sciatic nerve blockade, (*ARS*) 227P

Creagh-Barry, P. *see* Newton, D. E. F. 61–65

Crean, P. M. *see* Sampaio, M. M. 199–201

Crul, J. *see* van Beem, H. 610–615

Crul, J. F. *see* Smith, D. C. 206–209

Cunningham, A. J. *see* Claffey, L. P., (*ARS*) 234–235P; Patterson, K. W., (*ARS*) 222–223P

Dabbous, A. *see* Baraka, A 645–648

Dailland, P. *see* Lirzin, J. D. 641–644

Davidson, J. T. *see* Drenger, B. 82–86

Davies, C. A. *see* Hutchison, G. L. 518–521

Davies, C. J. *see* Stack, C. G., (*ARS*) 232P

Day, S J. *see* Dodd, P. 77–81

Deam, R. K. and Soni, N. Effects of pipecuronium and pancuronium on the isolated rabbit heart 287–289

De Andres, J. A. The blood lancet in regional anaesthesia, (*C*) 348

Debaene, B. *see* Meistelman, C., (*ARS*) 228–229P

Deloof, T. *see* Naeije, R. 532–539

Delrue, G. *see* Vangerven, M. 98–100

Denborough, M. A. *see* Foster, P. S. 560–565; 566–572

Derrington, M. C. Measurement of transdiaphragmatic pressure, (*C*) 238; Neuromuscular block in diaphragm and hand, (*C*) 236

Deschner, L. S. *see* Wilton, N. C. T. 434–438

Dewan, D. M. *see* James, F. M. iii, (*R*) 582

Diab, M. *see* Baraka, A. 645–648

Diedericks, J., Leone, B. J., Sear, J. W., Foex, P. and Ryder, W. A. Effect of nitrous oxide during basal propofol anaesthesia on myocardium with normal and critically restricted blood supply, (*ARS*) 224P

Dierdorf, S F. *see* Stoelting, R. K , (*R*) 471–472

Di Feo, G. *see* Celleno, D. 649–654

Di Rienzo, V. *see* Patriarca, G. 210–212

Dixon, J. *see* Tackley, R. M. 46–53

Dodd, P., Day, S. J., Goldhill, D R., MacLeod, D. M., Withington, P S. and Yate, P. M. Glycopyrronium requirements for antagonism of the muscarinic side effects of edrophonium 77–81

Donald, J. R. Spinal anaesthesia and surgical blood loss, (*C*) 114

Donaldson, R. *see* Kox, W., (*R*) 701

Donegan, J. H., (editor) *A Manual of Anaesthesia for Emergency Surgery*, 1st Edn, (*R*) 350

Donoso Bach, L. *see* Montero Matamala, A. 637–640

Doran, B. R. H. *see* Pollard, B. J. 95–97

Doré, C *see* Bellhouse, C. P., (*C*) 469

Doré, C. J. *see* Newton, D. E. F. 61–65

Dorrington, K. L. and McRae, K. M. Hyperventilation haemolysis: are humans at risk? (*ARS*) 235P

Douglas, R. H. B. *see* Whitfield, A. 694–696

Dowd, T. *see* Sweeney, J., (*ARS*) 222P

Drenger, B. Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy, (*C*) 580

Drenger, B., Shir, Y., Pode, D , Shapiro, A., Magora, F. and Davidson, J. T. Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy 82–86

Dresner, D. L. and Ali, H. H. Anaesthetic management of a patient with facioscapulohumeral muscular dystrophy 331–334

Dripps, R. D., Eckenhoff, J. E. and Vandam, L. D *Introduction to Anaesthesia: The Principles of Safe Practice*, 7th Edn, (*R*) 116–117

Drummond, G. B. Comparison of the effects of sedation with midazolam or ketamine on the airway muscles, (*ARS*) 230P

Drummond, G. B. *see* Pugh, G. C. 601–609; Ray, D C. 553–559

Dubreuil, C. *see* Chassard, D. 522–526

Dundee, J. W. and Milligan, K. R. Influence of alcohol consumption on the induction dose of thiopentone, (*ARS*) 229–230P

Dundee, J. W. and Wyant, G. M. *Intravenous Anaesthesia*, 2nd Edn. (*R*) 238

Dunnill, M. S. *see* Niblett, D. J. 628–636

Dwyer, R., Fee, J. P. H., Black, G. W. and Clarke, R. S. J. Comparison of increase in end-tidal concentrations of halothane and isoflurane in elderly patients, (*ARS*) 219–220P

Dykes, M. H. M. *see* Ovassapian, A. 13–16

Dzwonczyk, R. *see* McDonald, J. S., (*C*) 700

Eckenhoff, J. E. *see* Dripps, R. D., (*R*) 116–117

Edwards, M., Serrao, J. M., Gent, J. P. and Goodchild, C. S. GABA involvement in spinal analgesia with midazolam, (*ARS*) 233P

van Egmond, J. *see* van Beem, H 610–615
Elias, E. *see* Mills, C. O. 311–315
Ellis, F. R. *see* Christian, A. S. 540–544; Fairbrass, M. J. 66–69; Keeler, J. F., (*ARS*) 223–224P; Madej, T. H. 515–517
Ellis, H. and Fieldman, S., (editors) *Anatomy for Anaesthetists*, (*R*) 473
Elwell, A. *see* Canning, J., (*ARS*) 226P
Engbæk, J., Østergaard, D. and Viby-Mogensen, J. Double burst stimulation (DBS): a new pattern of nerve stimulation to identify residual neuromuscular block 274–278
Evans, R. D., Palazzo, M. G. A. and Ackers, J. W. L. Air embolism during total hip replacement: comparison of two surgical techniques 243–247
Ewart, M. *see* Best, C. J. 576–577

Fahy, L., Horton, W. A., Sprigge, J. S. and Charters, P. X-ray laryngoscopy in patients with a history of difficult laryngoscopy during pregnancy, (*ARS*) 234P
Fahy, L. *see* Horton, W. A. 6–12
Fairbrass, M. J., Coe, P. and Ellis, F. R. Adrenal cortical reserve in patients undergoing muscle biopsy for malignant hyperthermia screening 66–69
Fairley, H. B. *see* Marshall, B. E., (*R*) 473
Fais, G. *see* Patriarca, G. 210–212
Faithfull, N. S. Factors affecting headache following anaesthesia for urological daycase surgery, (*ARS*) 220–221P
Fassoulaki, A. Nasotracheal intubation, paranasal sinusitis and head injuries, (*C*) 236
Fassoulaki, A. and Vassiliou, M. Effect of oral midazolam and diazepam on some pulmonary function tests, (*ARS*) 232P
Fazackerley, E. J. *see* Randall, N. P. C. 159–163
Fee, J. P. H. *see* Dwyer, R., (*ARS*) 219–220P
Fell, D., Watson, A. P. and Hindocha, N. Plasma concentrations of catecholamines following intraocular irrigation with adrenaline 573–575
Fieldman, S. *see* Ellis, H., (*R*) 473
Finucane, B. T. and Santora, A. H., (authors) *Principles of Airway Management*, 1st Edn, (*R*) 116
Fletcher, J. E., Lizzo, F. H. and Rosenberg, H. Suxamethonium and malignant hyperthermia, (*C*) 468
Fletcher, M. E. *see* Stack, C. G., (*ARS*) 232P
Fletcher, R. Estimation of Pa_{CO_2} from end-tidal Pco_2 and Hb saturation in cyanotic children, (*ARS*) 231P; Relationship between alveolar deadspace and arterial oxygenation in children with congenital cardiac disease 168–176
Flynn, R. J., Moore, J., Collier, P. S. and McClean, E. Does pretreatment with cimetidine and ranitidine affect the disposition of bupivacaine? 87–91
Foex, P. *see* Diedericks, J., (*ARS*) 224P
Forbes, R. and Murray, D. J Teaching fibreoptic intubation, (*C*) 113–114
Ford, D. *see* Weeks, D B., (*C*) 237
Ford, G. C. *see* Carli, F., (*ARS*) 220P
Foster, P. S. and Denborough, M A. Effect of diltiazem and dantrolene on the contractility of isolated malignant hyperpyrexia-susceptible porcine skeletal muscle 566–572
Foster, P. S , Hopkinson, K. C. and Denborough, M. A. Effect of diltiazem on porcine malignant hyperpyrexia induced by suxamethonium and halothane 560–565
Foster, V. *see* Goudsouzian, N. G. 263–268
Franks, P. J., Hooper, R. H. and Jones, P. R. M. Solubility of Freon-22 in blood and lung tissue 425–428
Freeman, J F. *see* Mills, C. O. 311–315

Gamil, M. Serial peak expiratory flow rates in mothers during Caesarean section under extradural anaesthesia 415–418
Gandy, J. *see* Carli, F., (*ARS*) 220P
Gasparini, R. *see* van Beem, H. 610–615
Gent, J. P. *see* Edwards, M., (*ARS*) 233P; Serrao, J. M., (*ARS*) 233–234P
Glavin, R. J. *see* Lawson, D. H. 596–600
Gold, M. I. Preoxygenation, (*E*) 241
Goldhill, D. R. *see* Dodd, P. 77–81
Goodchild, C. S. *see* Edwards, M., (*ARS*) 233P, Serrao, J. M., (*ARS*) 233–234P
Goodman, N. W. The anaesthetist's activities in the operating theatre, (*C*) 700
Gordon, K. L. and Reilly, C S. Recovery of neuromuscular function after infusion or intermittent bolus doses of atracurium or vecuronium 269–273
Gottardis, M , Khunl-Brady, K. S., Koller, W , Sigl, G. and Hackl, J. M. Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations 393–396
Goudsouzian, N. G., Alifimoff, J. K., Liu, L M. P., Foster, V., McNulty, B. and Savarese, J. J. Neuromuscular and cardiovascular effects of doxacurium in children anaesthetized with halothane 263–268
Govenden, V. *see* Matthews, P. J. 204–205
Grant, I. S. *see* Reay, B. A. 248–252
Gray, I. G. *see* Hutchison, G. L. 518–521
Grundy, E. M. *see* Loughnan, B. A. 297–300
Guiraud, M. *see* Chassard, D. 522–526

Hackl, J. M. *see* Gottardis, M. 393–396
Hahn, C. E. W. *see* Sykes, M. K. 445–455
Hall, G. M. *see* Loughnan, B. A. 297–300
Halliday, D. *see* Carli, F., (*ARS*) 220P
Halsall, P. J. *see* Christian, A. S. 540–544; Madej, T. H. 515–517
Hand, C. W. *see* Sear, J. W. 22–27; 28–32
Hanna, A. N., McDonald, J. S., Miller, C. H. jr and Couri, D. Pretreatment with paracetamol inhibits metabolism of enflurane in rats 429–433
Hanning, C. D. *see* Reed, P. N. 316–318; Wilkins, C. J 439–444
Hansen, M., Bendixen, D., Poulson, M. and Hartmann, F. Nasotracheal intubation, paranasal sinusitis and head injuries, (*C*) 237
Harper, N. J. N. *see* Johnson, R. A. 483–487, Pollard, B. J. 95–97
Harris, S. *see* Jani, K., (*ARS*) 226–227P
Hartmann, F. *see* Hansen, M., (*C*) 237
Harvey, J. T. *see* Tackley, R. M. 46–53
Hatch, D. J. *see* Stack, C. G., (*ARS*) 232P
Hayes, J. D. *see* Ray, D. C. 553–559
Healy, T. E. J. *see* Middleton, C. M. 659–663; Randall, N. P. C. 159–163
Helbo-Hansen, S. *see* Toft, P. 319–320
Hetreed, M. J. *see* Loughnan, B. A., (*ARS*) 223P
Heykants, J. *see* van Beem, H. 610–615
Higgs, B. Measurement of transdiaphragmatic pressure, (*C*) 237–238
Hindocha, N. *see* Fell, D. 573–575; Jones, M. J. 124–128
Ho, A. M -H. Parkinsonism and the anaesthetist, (*C*) 580
Hodsman, N. B. A., Colvin, J. R. and Kenny, G. N. C. Effect of ketanserin on sodium nitroprusside requirements, arterial pressure control and heart rate following coronary artery bypass surgery 527–531
Hooper, R. H. *see* Franks, P. J. 425–428
Hopkins, C. S. and Leith, S. Acute gastric dilatation in an incarcerated hiatus hernia 108–111
Hopkinson, K. C. *see* Foster, P. S. 560–565
Horton, J. M. *see* Oh, T E., (*C*) 467–468

Horton, W. A., Fahy, L. and Charters, P. Defining a standard intubating position using "Angle Finder" 6–12
Horton, W. A. *see* Fahy, L., (*ARS*) 234P
Howells, T. H. *see* Ainsworth, Q. P. 494–497
Hull, C. J. The safety of new drugs, (*E*) 587–589
Hunter, J. M. *see* Parker, C. J. R. 177–183
Husegaard, H. C. *see* Nielsen, T. H. 164–167
Hutchison, G. L., Davies, C. A., Main, G. and Gray, I. G. Incidence of arrhythmias in dental anaesthesia: a cross-over comparison of halothane and isoflurane 518–521
Hutton, P. *see* Stokes, D. N. 202–203

Jackson, R. K. *see* Sykes, M. K. 445–455
Jacquinot, P. *see* Lirzin, J. D. 641–644
Jaffe, J. *see* Storella, R. J. 478–482
James, F. M. III, Wheeler, A. S. and Dewan, D. M., (editors) *Obstetric Anesthesia: The Complicated Patient*, 2nd Edn, (*R*) 582
James, M. F. M. Use of magnesium sulphate in the anaesthetic management of phaeochromocytoma: a review of 17 anaesthetics 616–623
James, M. F. M., Reyneke, C. J. and Whiffler, K. Heart block following propofol: a case report 213–215
Jana, N. *see* Biswas, C. 338–339
Jani, K., McEvedy, B., Harris, S. and Samaan, A. Maternal and neonatal bupivacaine concentrations after spinal and extradural anaesthesia for Caesarean section, (*ARS*) 226–227P
Jasson, J. *see* Lirzin, J. D. 641–644
Jensen, K., Bunemann, L., Riisager, S. and Thomsen, L. J. Cerebral blood flow during anaesthesia: influence of pretreatment with metoprolol or captopril 321–323
Jephcott, A. *A History of Longworth Scientific Instrument Co. Ltd*, 1st Edn, (*R*) 583
Jick, H., Andrews, E. B., Tilson, H. H., Pfanschmidt, M., Branche, C., Walker, A. M. and Lawson, D. H. Atracurium—a post-marketing surveillance study: methods and U.S. experience 590–595
Jick, H. *see* Lawson, D. H. 596–600
Johnson, R. A. and Harper, N. J. N. Antagonism of moderate degrees of vecuronium-induced neuromuscular block by small doses of neostigmine 483–487
Jones, J. G. *see* Cook, P. R. 402–408
Jones, M. J. and Mitchell, R. W. D. Prostaglandins and the lower oesophageal sphincter, (*C*) 581
Jones, M. J., Mitchell, R. W. D. and Hindocha, N. Effects on the lower oesophageal sphincter of cisapride given before the combined administration of atropine and neostigmine 124–128
Jones, P. R. M. *see* Franks, P. J. 425–428
Jonmarker, C. *see* Larsson, A. 378–384
Jorrot, J. C. *see* Lirzin, J. D. 641–644
Joubaud, A. *see* Chassard, D. 522–526
Juhl, B. *see* Schurizek, B. A. 129–137; 674–682

Kalli, I. Effect of surface electrode positioning on the compound action potential evoked by ulnar nerve stimulation in anaesthetized infants and children 188–193
Karliczek, R. *see* Wierda, J. M. K. H. 194–198
Katsuoka, M. and Ohnishi, S. T. Inhalation anaesthetics decrease calcium content of cardiac sarcoplasmic reticulum 669–673
Katz, J. *see* Snell, R. S., (*R*) 702
Kaufman, L., (editor) *Anaesthesia Review 5*, (*R*) 118
Kaur, N. *see* Ramachandra, V. 409–414
Kay, B. *see* Middleton, C. M. 659–663
Keeler, J. F. and Ellis, F. R. Estimation of core temperature by use of an insulated arm, (*ARS*) 223–224P
Keen, R. I. *see* Anderton, J. M., (*R*) 238
Kehlet, H. *see* Scott, N. B. 253–257
Keilty, S. R. *see* Sampaio, M. M. 199–201
Kendig, J. J. *see* MacIver, M. B. 301–310
Kenny, G. N. C. *see* Brockway, M. S., (*ARS*) 224–225P; Hodsman, N. B. A. 527–531
Ket, J. M. *see* Wierda, J. M. K. H. 194–198
Khuenl-Brady, K. S., Canfell, P. C., Miller, R. D., Castagnoli, K. P. and Agoston, S. Pharmacokinetics and disposition of Org 9616 and Org 9426 in the cat, (*ARS*) 225–226P
Khunl-Brady, K. S. *see* Gottardis, M. 393–396
Kidd, J. F. and Vickers, M. D. Pulse oximeters: essential monitors with limitations, (*E*) 355–357
King, M. J. *see* Loughnan, B. A. 297–300
Kinjo, M., Nagashima, H. and Vizi, E. S. Effect of atracurium and laudanosine on the release of ^{3}H-noradrenaline 683–690
Knudsen, F. *see* Tønnesen, E. 327–330
Kochi, T., Sako, S., Nishino, T. and Mizuguchi, T. Effect of high thoracic extradural anaesthesia on ventilatory response to hypercapnia in normal volunteers 362–367
Koller, W. *see* Gottardis, M. 393–396
Kong, K. L. *see* Martin, D. G. 456–461
Kosaka, F. *see* Ono, K. 324–326
Kottler, B. *see* Lenz, G., (*R*) 701–702
Kox, W., Boultbee, J. and Donaldson, R., (editors) *Imaging and Labelling Techniques in the Critically Ill*, (*R*) 701
Kraglund, K. *see* Schurizek, B. A. 129–137; 674–682
Krejcie, T. C. *see* Ovassapian, A. 13–16
Kristoffersen, E. *see* Nielsen, T. H. 164–167
Krivosic-Horber, R., Reyfort, H., Becq, M. C. and Adnet, P. Effect of propofol on the malignant hyperthermia susceptible pig model 691–693

Laishley, R. *see* Reynolds, F. 509–514
Lamb, K. S. R. *see* Stone, P. A. 335–337
de Lange, J. J. *see* Scheepstra, G. L. 92–94
Larsen, H. V. *see* Nielsen, T. H. 164–167
Larsson, A., Jonmarker, C., Lindahl, S. G. E. and Werner, O. Lung function in the supine and lateral decubitus positions in anaesthetized infants and children 378–384
Lawson, D. H., Paice, G. M., Glavin, R. J., Andrews, E. B., Branche, C., Tilson, H. and Jick, H. Atracurium—a post-marketing surveillance study: U.K. study and discussion 596–600
Lawson, D. H. *see* Jick, H. 590–595
Ledingham, I. McA., (editor) *Recent Advances in Critical Care Medicine*, Volume 3. (*R*) 118–119
Lee, A. *see* Reynolds, F. 509–514
Leeman, M. *see* Naeije, R. 532–539
Leith, S. *see* Hopkins, C. S. 108–111
Lejeune, P. *see* Naeije, R. 532–539
Lenz, G., Kottler, B., Schorer, R. and Spoerel, W. E., (editors) *Pocket Manual of Anesthesia*, 1st Edn, (*R*) 701–702
Leone, B. J. *see* Diedericks, J., (*ARS*) 224P
Leuwer, M. Significance of preload on mechanomyographic relaxometry in infants, children and adults, (*ARS*) 228P
Lewis, G. T. R. *see* Martin, D. G. 456–461, Tackley, R. M. 46–53
Lim, M. Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy, (*C*) 579
Lindahl, S. G. E. Oxygen consumption and carbon dioxide

elimination in infants and children during anaesthesia and surgery 70–76
Lindahl, S. G. E. *see* Larsson, A. 378–384
Lindgren, L. *see* Scheinin, B. 385–392
Lip, H. *see* Wierda, J. M. K. H. 194–198
Lirzin, J. D., Jacquinot, P., Dailland, P., Jorrot, J. C., Jasson, J., Talafre, M. L. and Conseiller, C. Controlled trial of extradural bupivacaine with fentanyl, morphine or placebo for pain relief in labour 641–644
Liu, L. M. P. *see* Goudsouzian, N. G. 263–268
Liu, N. *see* Meistelman, C., (*ARS*) 228–229P
Lizzo, F. H. *see* Fletcher, J. E., (*C*) 468
Longnecker, D. E. *see* Marshall, B. E., (*R*) 473
Loughlin, C. J. *see* Shah, N. K. 150–152
Loughnan, B. A., Anderson, S. J., Hetreed, M. J., Weston, P. and Boyd, S. G. Effects of halothane on electrically stimulated motor evoked potential in the extradural space, (*ARS*) 223P
Loughnan, B. A., King, M. J., Grundy, E. M., Young, D. L. and Hall, G. M. Effects of halothane on somatosensory evoked potentials recorded in the extradural space 297–300
Louis, F. *see* Baraka, A. 645–648
Ludgrove, T. *see* Braude, N. 101–103
Lund, C. *see* Scott, N. B. 253–257

McCafferty, D. F., Woolfson, A. D. and Boston, V. *In vivo* assessment of percutaneous local anaesthetic preparations 17–21
McCammon, R. L. *see* Stoelting, R. K., (*R*) 471–472
McClean, E. *see* Flynn, R. J. 87–91
McDonald, J. S. and Dzwonczyk, R. The anaesthetist's activities in the operating theatre, (*C*) 700
McDonald, J. S. *see* Hanna, A. N. 429–433
McEllistrem, R. F. *see* Patterson, K. W., (*ARS*) 222–223P
McEvedy, B. *see* Jani, K., (*ARS*) 226–227P
MacIver, M. B., Tauck, D. L. and Kendig, J. J. General anaesthetic modification of synaptic facilitation and long-term potentiation in hippocampus 301–310
MacKenzie, N. *see* Reay, B. A. 248–252
McKiernan, E. P. *see* Meakin, G. 655–658
MacLeod, D. M. *see* Dodd, P. 77–81
McLoughlin, C. Use of propofol in a patient with porphyria, (*C*) 114
McNulty, B. *see* Goudsouzian, N. G. 263–268
McQuay, H. J. *see* Sear, J. W. 22–27; 28–32
McRae, K. M. *see* Dorrington, K. L., (*ARS*) 235P
Macrae, W. A. *see* Reay, B. A. 248–252
Madej, T. H., Ellis, F. R. and Halsall, P. J. Evaluation of "3 in 1" lumbar plexus block in patients having muscle biopsy 515–517
Maestrone, E. *see* Wierda, J. M. K. H. 194–198
Magora, F. *see* Drenger, B. 82–86
Mahoney, A. Prostaglandins and the lower oesophageal sphincter, (*C*) 581
Main, G. *see* Hutchison, G. L. 518–521
Maitra, S. *see* Biswas, C. 338–339
Manabe, N. *see* Ono, K. 324–326
Manara, A. R., Shelly, M. P., Quinn, K. G. and Park, G. R. Pharmacokinetics of morphine following administration by the buccal route 498–502
Manara, A. R. *see* Park, G. R., (*R*) 116
Marcy, J. H. *see* Cook, D. R., (*R*) 472–473
Marshall, B. E., Longnecker, D. E. and Fairley, H. B., (editors) *Anaesthesia for Thoracic Procedures*, (*R*) 473
Martin, D. G., Kong, K. L. and Lewis, G. T. R. Resistance to airflow in anaesthetic breathing systems 456–461
Matthay, M. A. *see* Matthay, R. A., (*R*) 116
Matthay, R. A., Matthay, M. A. and Weidemann, H. P., (editors) *Annual Review of Pulmonary and Critical Care Medicine 88/89*, (*R*) 116
Matthews, P. J. and Govenden, V. Comparison of continuous paravertebral and extradural infusions of bupivacaine for pain relief after thoracotomy 204–205
Mayat, N. *see* Brock-Utne, J. G. 397–401
Meakin, G., McKiernan, E. P., Morris, P. and Baker, R. D. Dose–response curves for suxamethonium in neonates, infants and children 655–658
Mehr, E. *see* Storella, R. J. 478–482
Meijler, A. P. *Automation in Anesthesia—A Relief?* (*R*) 350
Meistelman, C., Spez, M., Liu, N., Debaene, B. and Saint-Maurice, C. Antagonism of vecuronium with neostigmine in children: influence of the associated halogenated agent, (*ARS*) 228–229P
Melot, C. *see* Naeije, R. 532–539
Meretoja, O. A. Is vecuronium a long-acting neuromuscular blocking agent in neonates and infants? 184–187
Merritt, H. *see* Carli, F., (*ARS*) 220P
van der Merwe, W. *see* Coetzee, A., (*R*) 471
Middleton, C. M., Pollard, B. J., Healy, T. E. J. and Kay, B. Use of atracurium or vecuronium to prolong the action of tubocurarine 659–663
Miles, M. *see* Prince, G. D. 503–508
Millar, S. W., Barnes, P. K., Soni, N. and Tennant, R. Comparison of the Magill and Lack anaesthetic breathing systems in anaesthetized patients 153–158
Miller, C. H. jr *see* Hanna, A. N. 429–433
Miller, R. D. *see* Khuenl-Brady, K. S., (*ARS*) 225–226P
Milligan, K. R. *see* Dundee, J. W., (*ARS*) 229–230P
Mills, C. O., Freeman, J. F., Salt, P. J. and Elias, E. Effect of anaesthetic agents on bile flow and biliary excretion of ^{131}I-cholylglycyltyrosine in the rat 311–315
Mirakhur, R. K. *see* Bell, P. F., (*ARS*) 225P
Mitchell, R. W. D., Bowler, G. M. R. and Scott, D. B. Spinal anaesthesia with bupivacaine, (*C*) 113
Mitchell, R. W. D. *see* Jones, M. J. 124–128; (*C*) 581
Mizuguchi, T. *see* Kochi, T. 362–367
Modla, C. Y. *see* Randall, N. P. C. 159–163
Mogensen, T. *see* Scott, N. B. 253–257
Montero Matamala, A., Vidal Lopez, F., Aguilar Sanchez, J. L. and Donoso Bach, L. Percutaneous anterior approach to the coeliac plexus using ultrasound 637–640
Moodley, J. *see* Brock-Utne, J. G. 397–401
Moore, C. *see* Ramachandra, V. 409–414
Moore, J. *see* Flynn, R. J. 87–91
Moore, R. A. *see* Sear, J. W. 22–27; 28–32
Moores, M. *see* Wilkins, C. J. 439–444
Morgan, B. *see* Reynolds, F. 509–514
Morita, K. *see* Ono, K. 324–326
Morris, P. *see* Meakin, G. 655–658
Moss, E. *see* Christys, A. R. 624–627
Mostafa, S. M. *see* Sweeney, J., (*ARS*) 222P
Murray, A. *see* Brockway, M. S., (*ARS*) 224–225P
Murray, D. J. *see* Forbes, R., (*C*) 113–114
Murray, J. P. *see* Patterson, K. W., (*ARS*) 222–223P
Myers, D. *see* Cook, P. R. 402–408

Naeije, R., Lejeune, P., Leeman, M., Melot, C. and Deloof, T. Effects of propofol on pulmonary and systemic arterial pressure–flow relationships in hyperoxic and hypoxic dogs 532–539
Nagashima, H. *see* Kinjo, M. 683–690
Neave, R. *see* Anderton, J. M., (*R*) 238
Nelson, T. E. Suxamethonium and malignant hyperthermia, (*C*) 468–469
Newton, D. E. F., Thornton, C., Creagh-Barry, P. and

Doré, C. J. Early cortical auditory evoked response in anaesthesia: comparison of the effects of nitrous oxide and isoflurane 61–65
Niblett, D. J., Sandhar, B. K., Dunnill, M. S and Sykes, M. K. Comparison of the effects of high frequency oscillation and controlled mechanical ventilation on hyaline membrane formation in a rabbit model of the neonatal respiratory distress syndrome 628–636
Nielsen, H. K. *see* Tønnesen, E 327–330
Nielsen, J. W. *see* Christensen, P. A. 258–262
Nielsen, T. H., Kristoffersen, E., Olsen, K. H., Larsen, H. V., Husegaard, H. C. and Wernberg, M. Plain bupivacaine: 0·5% or 0·25% for spinal analgesia? 164–167
Nishino, T. *see* Kochi, T. 362–367
Nisini, R. *see* Celleno, D. 649–654
Noble, H. A. *see* Wolf, A. R., (*ARS*) 221–222P
Noorduin, H. *see* van Beem, H. 610–615
Noreng, M. *see* Christensen, P. A. 258–262
Norman, J. *see* Scott, R. P. F., (*C*) 349; 373–377
Noueihid, R. *see* Baraka, A. 645–648
Nucera, E. *see* Patriarca, G. 210–212
Nunn, J. F *see* Royston, B. D. 419–424

Oh, T. E. and Horton, J. M. Adverse reactions to atracurium, (*C*) 467–468
Ohnishi, S. T. *see* Katsuoka, M. 669–673
Ohta, Y. *see* Ono, K. 324–326
Olsen, K. H. *see* Nielsen, T. H. 164–167
Ono, K., Manabe, N., Ohta, Y., Morita, K. and Kosaka, F. Influence of suxamethonium on the action of subsequently administered vecuronium or pancuronium 324–326
Ordman, A. J. and Payne, J. P. Decay in blood chloroform concentrations after anaesthesia, (*ARS*) 229P
Østergaard, D. *see* Engbæk, J. 274–278
O'Toole, D. P. *see* Claffey, L. P., (*ARS*) 234–235P
Ovassapian, A., Krejcie, T. C., Yelich, S. J. and Dykes, M. H. M. Awake fibreoptic intubation of the patient at high risk of aspiration 13–16

Paice, G. M. *see* Lawson, D. H. 596–600
Palayiwa, E. *see* Sykes, M. K. 445–455
Palazzo, M. G. A. *see* Evans, R. D. 243–247
Park, G. R. and Manara, A. R., (editors) *Intensive Care—Pocket Reference*, (*R*) 116
Park, G. R. *see* Manara, A. R. 498–502
Parker, C. J. R. and Hunter, J. M. Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis 177–183
Parsons, M. A. *see* Wright, P. J. 104–107
Patriarca, G., Nucera, E., Schiavino, D., Romano, A., Di Rienzo, V., Pellegrino, S. and Fais, G. Pancuronium allergy: a case report 210–212
Patterson, K. W., Casey, P. B., McEllistrem, R. F., Murray, J P. and Cunningham, A. J. Haemodynamic and oxgen saturation changes during upper gastrointestinal endoscopy: evaluation of propofol and midazolam sedation, (*ARS*) 222–223P
Paul, D. L. and Wildsmith, J. A. W. Extradural pressure following the injection of two volumes of bupivacaine 368–372
Payne, J. P. *see* Ordman, A. J., (*ARS*) 229P
Pellegrino, S. *see* Patriarca, G. 210–212
Pfanschmidt, M. *see* Jick, H. 590–595
Pleuvry, B. J. *see* Pollard, B. J. 664–668; Randall, N. P. C. 159–163
Pode, D. *see* Drenger, B. 82–86
Pollard, B. J., Harper, N. J. N. and Doran, B. R. H. Use of continuous prolonged administration of atracurium in the ITU to a patient with myasthenia gravis 95–97
Pollard, B. J., Randall, N. P. C. and Pleuvry, B. J. Doxapram and the neuromuscular junction 664–668
Pollard, B. J *see* Middleton, C. M. 659–663
Ponte, J. and Sadler, C. L. Effect of halothane, enflurane and isoflurane on carotid body chemoreceptor activity in the rabbit and the cat 33–40; Effect of thiopentone, etomidate and propofol on carotid body chemoreceptor activity in the rabbit and the cat 41–45
van Poorten, J F. *see* Stienstra, R., (*C*) 112–113
Poulson, M. *see* Hansen, M., (*C*) 237
Powell, D *see* Christys, A. R. 624–627
Powers, D. M. *see* Brandom, B. W. 488–493
Prescott, L. F. *see* Randall, N. P. C. 159–163
Prince, G D., Shetty, G. R. and Miles, M. Safety and efficacy of a low volume extradural test dose of bupivacaine in labour 503–508
Prys-Roberts, C. *see* Tackley, R. M. 46–53; Wolf, A. R., (*ARS*) 221–222P
Pugh, G. C., Brown, D. T. and Drummond, G. B. Effect of nalbuphine hydrochloride on the ventilatory and occlusion pressure responses to carbon dioxide in volunteers 601–609

Quinn, K. G. *see* Manara, A. R. 498–502

Rafferty, M. P. *see* Tyler, C. K. G. 462–466
Ramachandra, V., Moore, C., Kaur, N. and Carli, F. Effect of halothane, enflurane and isoflurane on body temperature during and after surgery 409–414
Ramachandra, V. *see* Carli, F., (*ARS*) 220P
Randall, N. P. C., Pleuvry, B J., Fazackerley, E. J., Modla, C. Y., Prescott, L. F. and Healy, T. E. J. Effect of oral doxapram on morphine-induced changes in the ventilatory response to carbon dioxide 159–163
Randall, N. P. C. *see* Pollard, B. J. 664–668
Rashkovsky, O. M. *see* Wierda, J. M. K. H. 194–198
Ray, D. C., Beckett, G. J., Hayes, J. D. and Drummond, G. B. Effect of nicardipine infusion on the release of glutathione S-transferase following halothane anaesthesia 553–559
Read, M. *see* Carli, F., (*ARS*) 220P
Reay, B. A., Semple, A J., Macrae, W A., MacKenzie, N. and Grant, I S. Low-dose intrathecal diamorphine analgesia following major orthopaedic surgery 248–252
Reed, P. N., Colquhoun, A. D. and Hanning, C. D. Maternal oxygenation during normal labour 316–318
Reilly, C. S. *see* Gordon, K. L. 269–273
Reyfort, H. *see* Krivosic-Horber, R. 691–693
Reyneke, C. J *see* James, M. F. M. 213–215
Reynolds, F., Laishley, R , Morgan, B. and Lee, A. Effect of time and adrenaline on the feto-maternal distribution of bupivacaine 509–514
Ridley, S. *see* Stack, C. G., (*ARS*) 232P
Riisager, S. *see* Jensen, K. 321–323
Robson, N. *see* Stokes, D. N. 202–203
Rogers, M., (editor) *Current Practice in Anesthesiology*, 1st Edn, (*R*) 584
Rogers, M. C., (editor) *Yearbook of Critical Care Medicine, 1988*, 6th Edn, (*R*) 582
Romano, A. *see* Patriarca, G. 210–212
Ros, H. H *see* Scheepstra, G. L. 92–94
Rosen, M and Sanders, L. The Recovery Interest Group, (*C*) 470
Rosenberg, H. *see* Fletcher, J. E., (*C*) 468; Storella, R. J. 478–482
Rosenberg, P. H. *see* Tuominen, M. 358–361
Rout, C. *see* Brock-Utne, J. G. 397–401
Rowbotham, D. J. Cisapride and anaesthesia, (*E*) 121–123

Royston, B. D., Bottiglieri, T. and Nunn, J. F. Short term effect of nitrous oxide on methionine and S-adenosyl methionine concentrations 419–424
Rutten, C. L. G. *see* Scheepstra, G. L. 54–60
Ryan Cook, D. *see* Brandom, B. W. 488–493
Ryder, W. A. *see* Diedericks, J., (*ARS*) 224P

Sadler, C. L. *see* Ponte, J. 33–40; 41–45
Saint-Maurice, C. *see* Meistelman, C., (*ARS*) 228–229P
Sako, S. *see* Kochi, T. 362–367
Salim, M., (editor) *Acupuncture Treatment and Anaesthesia*, 4th Edn, (*R*) 702
Salt, P. J. *see* Mills, C. O. 311–315
Samaan, A. *see* Jani, K., (*ARS*) 226–227P
Sampaio, M. M., Crean, P. M., Keilty, S. R. and Black, G. W. Changes in oxygen saturation during inhalation induction of anaesthesia in children 199–201
Samuels, S. I. and Brodsky, J. B. Profound intraoperative atelectasis 216–218
Sanders, L. *see* Rosen, M., (*C*) 470
Sandhar, B. K. *see* Niblett, D. J. 628–636
Santora, A. H. *see* Finucane, B. T., (*R*) 116
Savarese, J J. *see* Goudsouzian, N. G 263–268
Scheepstra, G. L., Booij, L. H. D. J., Rutten, C. L. G. and Coenen, L. G J. Propofol for induction and maintenance of anaesthesia: comparison between younger and older patients 54–60
Scheepstra, G. L., de Lange, J. J., Booij, L. H. D. J. and Ros, H H. Median nerve evoked potentials during propofol anaesthesia 92–94
Scheinin, B., Scheinin, M., Vuorinen, J. and Lindgren, L. Alfentanil obtunds the cardiovascular and sympathoadrenal responses to suxamethonium-facilitated laryngoscopy and intubation 385–392
Scheinin, M. *see* Scheinin, B. 385–392
Schell, J. *see* Claffey, L. P., (*ARS*) 234–235P
Scheller, M. S. *see* Tateishi, A. 548–552
Schiavino, D. *see* Patriarca, G. 210–212
Schlichtig, R. *see* Ayres, S. M., (*R*) 117
Schorer, R. *see* Lenz, G., (*R*) 701–702
Schurizek, B. A , Willacy, L H. O , Kraglund, K., Andreasen, F. and Juhl, B. Antroduodenal motility, pH and gastric emptying during balanced anaesthesia: comparison of pethidine and fentanyl 674–682; Effects of general anaesthesia with halothane on antroduodenal motility, pH and gastric emptying rate in man 129–137
Schuttler, J. *see* Schwilden, H. 290–296
Schwilden, H., Stoeckel, H. and Schuttler, J. Closed-loop feedback control of propofol anaesthesia by quantitative EEG analysis in humans 290–296
Scott, D. B., (editor) *Diamorphine · Its Chemistry, Pharmacology and Clinical Use*, (*R*) 117; Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, (*C*) 578; Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, (*C*) 579
Scott, D. B. *see* Mitchell, R. W D., (*C*) 113
Scott, N. B., Mogensen, T., Bigler, D., Lund, C and Kehlet, H. Continuous thoracic extradural 0 5% bupivacaine with or without morphine: effect on quality of blockade, lung function and the surgical stress response 253–257
Scott, R. P. F. and Norman, J. Doxacurium chloride · a preliminary clinical trial 373–377; Effect of suxamethonium given during recovery from atracurium, (*C*) 349
Sear, J. W., Hand, C. W., Moore, R. A. and McQuay, H. J. Studies on morphine disposition: influence of general anaesthesia on plasma concentrations of morphine and its metabolites 22–27; Studies on morphine disposition: influence of renal failure on the kinetics of morphine and its metabolites 28–32
Sear, J. W. *see* Diedericks, J., (*ARS*) 224P
Semple, A. J. *see* Reay, B. A. 248–252
Serrao, J. M., Gent, J. P. and Goodchild, C. S. Naloxone antagonizes the spinal analgesic effects of midazolam, (*ARS*) 233–234P
Serrao, J. M. *see* Edwards, M., (*ARS*) 233P
Severn, A. M. Parkinsonism and the anaesthetist, (*C*) 580–581
Sfez, M. *see* Meistelman, C., (*ARS*) 228–229P
Shah, N K., Loughlin, C. J. and Bedford, R. F. Comparison of the Bain and the ADE systems during controlled ventilation in adults 150–152
Shapiro, A. *see* Drenger, B. 82–86
Sheikh, A. *see* Tunstall, M. E. 138–143
Shelly, M. P. *see* Manara, A. R. 498–502
Shetty, G. R. *see* Prince, G. D. 503–508
Shir, Y. *see* Drenger, B. 82–86
Shortland, J. R. *see* Wright, P. J. 104–107
Sibai, A. *see* Baraka, A. 645–648
Sigl, G. *see* Gottardis, M. 393–396
Simpson, P. J. *see* Carrie, L. E. S., (*R*) 472
Smith, D. C. and Crul, J. F. Oxygen desaturation following sedation for regional analgesia 206–209
Smith, G. Spinal anaesthesia and surgical blood loss, (*C*) 115
Snell, R. S. and Katz, J., (editors) *Clinical Anatomy for Anesthesiologists*, (*R*) 702
Soni, N. *see* Deam, R. K. 287–289; Millar, S. W. 153–158
Soni, N C. *see* Bruce, W. C. 144–149
Sosis, A. Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, (*C*) 578
Spiegelhalter, D. J. *see* Wilson, M. E., (*C*) 469
Spoerel, W. E. *see* Lenz, G., (*R*) 701–702
Sprigge, J. S. *see* Fahy, L., (*ARS*) 234P
Stack, C. G., Fletcher, M. E., Stocks, J., Davies, C. J., Ridley, S. and Hatch, D. J. Comparison of total ventilatory compliance in sedated and anaesthetized infants and young children, (*ARS*) 232P
Stell, P. M. *see* Campbell, I. T., (*ARS*) 231–232P
Sterling, M. J. *see* Ayres, S. M., (*R*) 117
Stevens, J. D. *see* Wright, P. J. 104–107
Stienstra, R. and van Poorten, J. F. Spinal anaesthesia with bupivacaine, (*C*) 112–113
Stirt, J. A. Accelerated recovery from combined atracurium–vecuronium neuromuscular block 697–699
Stocks, J. *see* Stack, C. G., (*ARS*) 232P
Stoeckel, H *see* Schwilden, H. 290–296
Stoelting, R. K., Dierdorf, S. F. and McCammon, R. L., (editors) *Anesthesia and Co-Existing Disease*, 2nd Edn, (*R*) 471–472
Stokes, D. N., Robson, N. and Hutton, P. Effect of diluting propofol on the incidence of pain on injection and venous sequelae 202–203
Stone, P. A., Thorburn, J. and Lamb, K. S. R. Complications of spinal anaesthesia following extradural block for Caesarean section 335–337
Storella, R. J., Jaffe, J., Mehr, E. and Rosenberg, H. *In vitro* investigation of the priming principle for rapid neuromuscular block 478–482
Sugg, B. R. *see* Sykes, M. K. 445–455
Sumner, E. *see* Best, C. J. 576–577
Sury, M. R. J. and Cole, P. V. Hypotensive agents: an animal model, (*C*) 112
Sweeney, J., Underhill, S., Dowd, T and Mostafa, S. M. Effects of fentanyl and alfentanil on the change in intraocular pressure produced by suxamethonium and tracheal intubation, (*ARS*) 222P
Sykes, M. K. High frequency ventilation, (*E*) 475–477
Sykes, M. K., Sugg, B. R., Hahn, C. E. W., Jackson, R. K. and Palayiwa, E. A new microprocessor-controlled anaesthetic machine 445–455
Sykes, M. K. *see* Niblett, D. J. 628–636

Tackley, R. M., Lewis, G. T. R., Prys-Roberts, C., Boaden, R. W., Dixon, J. and Harvey, J. T. Computer controlled infusion of propofol 46–53
Taivainen, T. *see* Tuominen, M. 358–361
Talafre, M. L. *see* Lirzin, J. D. 641–644
Tateishi, A., Zornow, M. H., Scheller, M. S. and Canfell, P. C. Electroencephalographic effects of laudanosine in an animal model of epilepsy 548–552
Tauck, D. L. *see* MacIver, M. B. 301–310
Taylor, P. M. Effect of dobutamine infusion on the adrenocortical response to halothane anaesthesia in ponies, (*ARS*) 219P
Tennant, R. *see* Millar, S. W. 153–158
Terrar, D. A. *see* Victory, J. G. G., (*ARS*) 227–228P
Thomsen, L. J. *see* Jensen, K. 321–323
Thorburn, J. Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, (*C*) 578–579
Thorburn, J. *see* Stone, P. A. 335–337
Thornton, C. *see* Newton, D. E. F. 61–65
Tilson, H. *see* Lawson, D. H. 596–600
Tilson, H. H. *see* Jick, H. 590–595
Todd, J. G. *see* Coventry, D. M., (*ARS*) 227P
Toft, P. and Helbo-Hansen, S. Interaction of ketamine with atracurium 319–320
Tomassetti, M. *see* Celleno, D. 649–654
Tønnesen, E., Knudsen, F., Nielsen, H. K. and Christensen, N. J. Natural killer cell activity in a patient undergoing resection of phaeochromocytoma 327–330
Tormey, W. *see* Claffey, L. P., (*ARS*) 234–235P
Traber, K. B. *see* Wilton, N. C. T. 434–438
Tunstall, M. E. and Sheikh, A. Comparison of 1.5% enflurane with 1 25% isoflurane in oxygen for Caesarean section: avoidance of awareness without nitrous oxide 138–143
Tuominen, M., Taivainen, T. and Rosenberg, P. H. Spread of spinal anaesthesia with plain 0.5% bupivacaine: influence of the vertebral interspace used for injection 358–361
Turner, G. A., Williams, J. D. and Baker, D. J. Train-of-four fade during onset and recovery of neuromuscular block: a study in non-anaesthetized subjects 279–286
Tyler, C. K. G., Barnes, P. K. and Rafferty, M. P. Controlled ventilation with a Mapleson A (Magill) breathing system: reassessment using a lung model 462–466

Underhill, S. *see* Sweeney, J., (*ARS*) 222P

Vandam, L. D. *see* Dripps, R. D., (*R*) 116–117
Vangerven, M., Delrue, G., Brugman, E. and Cosaert, P. A new therapeutic approach to accidental intra-arterial injection of thiopentone 98–100
Van Peer, A. *see* van Beem, H 610–615
Vassiliou, M. *see* Fassoulaki, A., (*ARS*) 232P
Vaughan, R. S. Airways revisited, (*E*) 1–3
Venn, P. J. H. Evaluation of the Ambu CPAP system 340–347
Viby-Mogensen, J. *see* Engbæk, J. 274–278
Vickers, M. D. *see* Kidd, J. F., (*E*) 355–357
Victory, J. G. G. and Terrar, D. A. Effects of bupivacaine on inward currents and contraction in single myocytes isolated from guineapig ventricle, (*ARS*) 227–228P
Vidal Lopez, F. *see* Montero Matamala, A. 637–640
Vizi, E. S. *see* Kinjo, M. 683–690
Vuorinen, J. *see* Scheinin, B. 385–392

Walker, A. M. *see* Jick, H. 590–595
Ward, S. *see* Canning, J., (*ARS*) 226P
Watkins, J *see* Wright, P. J. 104–107
Watson, A. P. *see* Fell, D. 573–575
Watters, C. H. *see* Campbell, W. I. 545–547
Waud, B. E. Neuromuscular block in diaphragm and hand, (*C*) 236
Weakly, J. N. *see* Brandom, B. W. 488–493
Weber, S. *see* Brandom, B. W. 488–493
Weeks, D. B. and Ford, D. Prolonged suxamethonium-induced neuromuscular block associated with organophosphate poisoning, (*C*) 237
Weidemann, H. P. *see* Matthay, R. A., (*R*) 116
Weller, R. *see* Baskett, P., (*R*) 117–118
Welsh, B. E. Aid to intubation, (*C*) 469–470
Wernberg, M. *see* Nielsen, T. H. 164–167
Werner, O. *see* Larsson, A. 378–384
Weston, P. *see* Loughnan, B. A., (*ARS*) 223P
Wheeler, A. S. *see* James, F. M. III, (*R*) 582
Whiffler, K. *see* James, M F M. 213–215
Whitfield, A. and Douglas, R. H. B. Effect of general anaesthesia on the magnetic resonance imaging signal from the brain 694–696
Whitten, C. E. *Anyone Can Intubate*, (*R*) 583
Wierda, J. M. K. H., Maestrone, E., Bencini, A. F., Boyer, A., Rashkovsky, O. M., Lip, H., Karliczek, R., Ket, J. M. and Agoston, S. Haemodynamic effects of vecuronium 194–198
Wildsmith, J. A. W. I. Predicting the spread of spinal anaesthesia, (*E*) 353–354
Wildsmith, J. A. W. *see* Paul, D. L. 368–372
Wilkins, C. J., Moores, M. and Hanning, C. D. Comparison of pulse oximeters: effects of vasoconstriction and venous engorgement 439–444
Willacy, L. H. O. *see* Schurizek, B. A. 129–137; 674–682
Willatt, D J. *see* Campbell, I. T., (*ARS*) 231–232P
Williams, J. D. *see* Turner, G. A 279–286
Wilson, G. *A Bibliography of References to Anaesthesia in the Australian Medical Journals 1846–1952*, (*R*) 350–351
Wilson, M. E. and Spiegelhalter, D. J. Predicting difficult intubation, (*C*) 469
Wilton, N. C. T., Traber, K. B. and Deschner, L. S. Anaesthetic management for Caesarean section in a patient with uncorrected truncus arteriosus 434–438
Wishart, H. Y. *see* Worsley, M. H., (*C*) 114
Withington, P. S. *see* Dodd, P. 77–81
Woelfel, S. K. *see* Brandom, B. W. 488–493
Woestenborghs, R. *see* van Beem, H. 610–615
Wolf, A. R., Carlisle, K. M., Noble, H. A. and Prys-Roberts, C. Evaluation of a bupivacaine–morphine mixture for caudal analgesia in children, (*ARS*) 221–222P
Wolff, G. *see* Brunner, J. X., (*R*) 351
Woolfson, A. D. *see* McCafferty, D. F. 17–21
Worsley, M. H., Wishart, H. Y. and Aitkenhead, A. R Spinal anaesthesia and surgical blood loss, (*C*) 114
Wright, P. J., Shortland, J. R., Stevens, J. D., Parsons, M. A. and Watkins, J. Fatal haemopathological consequences of general anaesthesia 104–107
Wyant, G. M. *see* Dundee, J. W., (*R*) 238

Yate, P. M. *see* Dodd, P. 77–81
Yelich, S J. *see* Ovassapian, A. 13–16
Young, D. L. *see* Loughnan, B. A. 297–300
Young, S. Effects of halothane, isoflurane and enflurane anaesthesia on the total ventilatory impedance of ponies, (*ARS*) 230–231P

Zorab, J. S. M., (editor) *Surgery for Anaesthetists*, (*R*) 471
Zornow, M. H. *see* Tateishi, A. 548–552

SUBJECT INDEX

A Bibliography of References to Anaesthesia in the Australian Medical Journals 1846–1952, Wilson, G., (*R*) 350–351
A History of Longworth Scientific Instrument Co. Ltd, 1st Edn, Jephcott, A., (*R*) 583
A Manual of Anaesthesia for Emergency Surgery, 1st Edn, Donegan, J. H., (editor), (*R*) 350
Abdominal pain, Percutaneous anterior approach to the coeliac plexus using ultrasound, Montero Matamala, A., *et al.* 637–640
Acetaminophen, Pretreatment with paracetamol inhibits metabolism of enflurane in rats, Hanna, A. N., *et al.* 429–433
Acetylcholinesterase, Doxapram and the neuromuscular junction, Pollard, B. J., *et al.* 664–668
Acupuncture Treatment and Anaesthesia, 4th Edn, Salim, M., (editor), (*R*) 702
Adductor pollicis muscle, Train-of-four fade during onset and recovery of neuromuscular block: a study in non-anaesthetized subjects, Turner, G. A., *et al.* 279–286
ADE system, Comparison of the Bain and the ADE systems during controlled ventilation in adults, Shah, N. K., *et al.* 150–152
Adrenal cortical reserve, Adrenal cortical reserve in patients undergoing muscle biopsy for malignant hyperthermia screening, Fairbrass, M. J., *et al.* 66–69
Adrenaline, Effect of time and adrenaline on the feto-maternal distribution of bupivacaine, Reynolds, F., *et al.* 509–514
——, Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, Scott, D. B., (*C*) 578
——, Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, Scott, D. B., (*C*) 579
——, Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, Sosis, A., (*C*) 578
——, Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, Thorburn, J., (*C*) 578–579
——, Plasma concentrations of catecholamines following intraocular irrigation with adrenaline, Fell, D., *et al.* 573–575
Adrenergic block, Use of magnesium sulphate in the anaesthetic management of phaeochromocytoma: a review of 17 anaesthetics, James, M. F. M. 616–623
Adrenocortical response, Effect of dobutamine infusion on the adrenocortical response to halothane anaesthesia in ponies, Taylor, P. M., (*ARS*) 219P
Adverse effects, Atracurium—a post-marketing surveillance study: methods and U.S. experience, Jick, H., *et al.* 590–595
——, Atracurium—a post-marketing surveillance study: U.K. study and discussion, Lawson, D. H., *et al.* 596–600
Adverse reactions, Adverse reactions to atracurium, Oh, T. E., *et al.*, (*C*) 467–468
Age, Oxygen consumption and carbon dioxide elimination in infants and children during anaesthesia and surgery, Lindahl, S. G. E. 70–76
——, Pharmacokinetics of alfentanil during and after a fixed rate infusion, van Beem, H., *et al.* 610–615
——, Propofol for induction and maintenance of anaesthesia: comparison between younger and older patients, Scheepstra, G. L., *et al.* 54–60
Aggregate anaphylaxis, Fatal haemopathological consequences of general anaesthesia, Wright, P. J., *et al.* 104–107
Air embolism, Air embolism during total hip replacement: comparison of two surgical techniques, Evans, R. D., *et al.* 243–247
Airflow resistance, Resistance to airflow in anaesthetic breathing systems, Martin, D. G., *et al.* 456–461
Airway muscles, Comparison of the effects of sedation with midazolam or ketamine on the airway muscles, Drummond, G. B., (*ARS*) 230P
Airways, Airways revisited, Vaughan, R. S., (*E*) 1–3
Alanine aminotransferase, Pretreatment with paracetamol inhibits metabolism of enflurane in rats, Hanna, A. N., *et al.* 429–433
Alcohol consumption, Influence of alcohol consumption on the induction dose of thiopentone, Dundee, J. W., *et al.*, (*ARS*) 229–230P
Alfentanil, Alfentanil obtunds the cardiovascular and sympathoadrenal responses to suxamethonium-facilitated laryngoscopy and intubation, Scheinin, B., *et al.* 385–392
——, Cardiovascular and respiratory effects of ketorolac and alfentanil during anaesthesia, Brockway, M. S., *et al.*, (*ARS*) 224–225P
——, Effects of fentanyl and alfentanil on the change in intraocular pressure produced by suxamethonium and tracheal intubation, Sweeney, J., *et al.*, (*ARS*) 222P
——, Pharmacokinetics of alfentanil during and after a fixed rate infusion, van Beem, H., *et al.* 610–615
Alkalaemic haemolysis, Hyperventilation haemolysis: are humans at risk? Dorrington, K. L., *et al.*, (*ARS*) 235P
Alkalinization, Alkalinization of bupivacaine for sciatic nerve blockade, Coventry, D. M., *et al.*, (*ARS*) 227P
Allergy, Fatal haemopathological consequences of general anaesthesia, Wright, P. J., *et al.* 104–107
——, Pancuronium allergy: a case report, Patriarca, G., *et al.* 210–212
Althesin, Effect of anaesthetic agents on bile flow and biliary excretion of ^{131}I-cholylglycyltyrosine in the rat, Mills, C. O., *et al.* 311–315
Alveolar deadspace, Relationship between alveolar deadspace and arterial oxygenation in children with congenital cardiac disease, Fletcher, R. 168–176
Ambu CPAP system, Evaluation of the Ambu CPAP system, Venn, P. J. H. 340–347
Amethocaine, *In vivo* assessment of percutaneous local anaesthetic preparations, McCafferty, D. F., *et al.* 17–21
An Introduction to Anaesthesiology, Coetzee, A., *et al.*, (editors), (*R*) 471
Anaesthesia for Thoracic Procedures, Marshall, B. E., *et al.*, (editors), (*R*) 473
Anaesthesia Review 5, Kaufman, L., (editor), (*R*) 118
Anaesthetic machine, A new microprocessor-controlled anaesthetic machine, Sykes, M. K., *et al.* 445–455
Anaesthetist's activities, The anaesthetist's activities in the operating theatre, Goodman, N. W., (*C*) 700
——, The anaesthetist's activities in the operating theatre, McDonald, J. S., *et al.*, (*C*) 700

Anaphylactic shock, Pancuronium allergy: a case report, Patriarca, G., *et al.* 210–212

Anatomy for Anaesthetists, Ellis, H., *et al.*, (editors), (*R*) 473

Anesthesia and Co-Existing Disease, 2nd Edn, Stoelting, R. K., *et al.*, (editors), (*R*) 471–472

Angiotensin converting enzyme (ACE) inhibition, Cerebral blood flow during anaesthesia: influence of pretreatment with metoprolol or captopril, Jensen, K., *et al.* 321–323

Animal model, Hypotensive agents: an animal model, Bagshaw, R. J., (*C*) 112

——, Hypotensive agents: an animal model, Sury, M. R. J., *et al.*, (*C*) 112

——, Teaching fibreoptic intubation, Forbes, R., *et al.*, (*C*) 113–114

Annual Review of Pulmonary and Critical Care Medicine 88/89, Matthay, R. A., *et al.*, (editors), (*R*) 116

Antagonism of neuromuscular blockade, Glycopyrronium requirements for antagonism of the muscarinic side effects of edrophonium, Dodd, P., *et al.* 77–81

Antibiotics, Perioperative complications following the use of vancomycin in children: a report of two cases, Best, C. J., *et al.* 576–577

Antinociceptive effects, Naloxone antagonizes the spinal analgesic effects of midazolam, Serrao, J. M., *et al.*, (*ARS*) 233–234P

Antroduodenal motility, Antroduodenal motility, pH and gastric emptying during balanced anaesthesia: comparison of pethidine and fentanyl, Schurizek, B. A., *et al.* 674–682

——, Effects of general anaesthesia with halothane on antroduodenal motility, pH and gastric emptying rate in man, Schurizek, B. A., *et al.* 129–137

Anyone Can Intubate, Whitten, C. E., (*R*) 583

Apnoea, Prolonged suxamethonium-induced neuromuscular block associated with organophosphate poisoning, Weeks, D. B., *et al.*, (*C*) 237

Arrhythmias, Incidence of arrhythmias in dental anaesthesia: a cross-over comparison of halothane and isoflurane, Hutchison, G. L., *et al.* 518–521

Arterial hypoxaemia, Relationship between alveolar deadspace and arterial oxygenation in children with congenital cardiac disease, Fletcher, R. 168–176

Arterial oxygenation, Arterial oxygenation after different types of major head and neck surgery, Campbell, I. T., *et al.*, (*ARS*) 231–232P

Arterial oxyhaemoglobin saturation (Sa_{O_2}), Maternal oxygenation during normal labour, Reed, P. N., *et al.* 316–318

Arterial pressure, Effect of ketanserin on sodium nitroprusside requirements, arterial pressure control and heart rate following coronary artery bypass surgery, Hodsman, N. B. A., *et al.* 527–531

Aspartate aminotransferase, Pretreatment with paracetamol inhibits metabolism of enflurane in rats, Hanna, A. N., *et al.* 429–433

Aspiration, Awake fibreoptic intubation of the patient at high risk of aspiration, Ovassapian, A., *et al.* 13–16

Atelectasis, Profound intraoperative atelectasis, Samuels, S. I., *et al.* 216–218

Atracurium, Accelerated recovery from combined atracurium–vecuronium neuromuscular block, Stirt, J. A. 697–699

——, Adverse reactions to atracurium, Oh, T. E., *et al.*, (*C*) 467–468

——, Anaesthetic management of a patient with facioscapulohumeral muscular dystrophy, Dresner, D. L., *et al* 331–334

——, Atracurium—a post-marketing surveillance study: methods and U.S. experience, Jick, H., *et al.* 590–595

——, Atracurium—a post-marketing surveillance study: U.K. study and discussion, Lawson, D. H., *et al.* 596–600

——, Effect of atracurium and laudanosine on the release of ^{3}H-noradrenaline, Kinjo, M., *et al.* 683–690

——, Effect of suxamethonium given during recovery from atracurium, Black, A. M. S., (*C*) 348–349

——, Effect of suxamethonium given during recovery from atracurium, Scott, R. P. F., *et al*, (*C*) 349

——, Electroencephalographic effects of laudanosine in an animal model of epilepsy, Tateishi, A., *et al.* 548–552

——, Interaction of ketamine with atracurium, Toft, P., *et al.* 319–320

——, Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis, Parker, C. J. R., *et al.* 177–183

——, Recovery of neuromuscular function after infusion or intermittent bolus doses of atracurium or vecuronium, Gordon, K. L., *et al.* 269–273

——, Use of atracurium or vecuronium to prolong the action of tubocurarine, Middleton, C. M., *et al.* 659–663

——, Use of continuous prolonged administration of atracurium in the ITU to a patient with myasthenia gravis, Pollard, B. J., *et al.* 95–97

Atropine, Effects on the lower oesophageal sphincter of cisapride given before the combined administration of atropine and neostigmine, Jones, M. J., *et al.* 124–128

——, Haemodynamic effects of vecuronium, Wierda, J. M. K. H., *et al.* 194–198

Auditory evoked potentials, Auditory evoked potentials during propofol anaesthesia in man, Chassard, D., *et al.* 522–526

Automation in Anesthesia—A Relief?, Meijler, A. P., (*R*) 350

Awake intubation, Awake fibreoptic intubation of the patient at high risk of aspiration, Ovassapian, A., *et al.* 13–16

Awareness, Awareness following different techniques of general anaesthesia for Caesarean section, Baraka, A., *et al.* 645–648

——, Comparison of 1.5% enflurane with 1.25% isoflurane in oxygen for Caesarean section: avoidance of awareness without nitrous oxide, Tunstall, M. E., *et al.* 138–143

Bain system, Comparison of the Bain and the ADE systems during controlled ventilation in adults, Shah, N. K., *et al.* 150–152

Barbiturate anaesthesia, Antroduodenal motility, pH and gastric emptying during balanced anaesthesia: comparison of pethidine and fentanyl, Schurizek, B. A., *et al.* 674–682

Baricity, Spinal anaesthesia with bupivacaine, Mitchell, R. W. D., *et al.*, (*C*) 113

——, Spinal anaesthesia with bupivacaine, Stienstra, R., *et al.*, (*C*) 112–113

Beta-adrenergic blocking agents, Cerebral blood flow during anaesthesia: influence of pretreatment with metoprolol or captopril, Jensen, K., *et al.* 321–323

Bicuculline, GABA involvement in spinal analgesia with midazolam, Edwards, M., *et al*, (*ARS*) 233P

Bilateral pneumothorax, Bilateral pneumothorax following tracheal intubation, Biswas, C., *et al.* 338–339

Bile flow, Effect of anaesthetic agents on bile flow and biliary excretion of ^{131}I-cholylglycyltyrosine in the rat, Mills, C. O., *et al.* 311–315

Biliary excretion, Effect of anaesthetic agents on bile flow and biliary excretion of ^{131}I-cholylglycyltyrosine in the rat, Mills, C. O., *et al.* 311–315

Biotransformation, Pretreatment with paracetamol inhibits metabolism of enflurane in rats, Hanna, A. N., *et al.* 429–433

Bite-block, Aid to intubation, Welsh, B. E., (*C*) 469–470

Blood–brain barrier, Blood–brain barrier to pertechnetate following drug-induced hypotension, Cook, P. R., *et al.* 402–408

Blood chloroform concentrations, Decay in blood chloroform concentrations after anaesthesia, Ordman, A. J., *et al.*, (*ARS*) 229P

Blood:CSF glycine, Blood:CSF glycine concentration gradient following a controlled i.v. infusion in dogs, Claffey, L. P., *et al.*, (*ARS*) 234–235P

Blood lancet, The blood lancet in regional anaesthesia, De Andres, J. A., (*C*) 348

Blood loss, Spinal anaesthesia and surgical blood loss, Donald, J. R., (*C*) 114

——, Spinal anaesthesia and surgical blood loss, Smith, G., (*C*) 115

——, Spinal anaesthesia and surgical blood loss, Worsley, M. H., *et al.*, (*C*) 114

Body temperature, Effect of halothane, enflurane and isoflurane on body temperature during and after surgery, Ramachandra, V., *et al.* 409–414

Bolus administration, Comparison of mivacurium and suxamethonium administered by bolus and infusion, Brandom, B. W., *et al.* 488–493

——, Recovery of neuromuscular function after infusion or intermittent bolus doses of atracurium or vecuronium, Gordon, K. L., *et al.* 269–273

Book Reviews

A Bibliography of References to Anaesthesia in the Australian Medical Journals 1846–1952, Wilson, G., (*R*) 350–351

A History of Longworth Scientific Instrument Co. Ltd, 1st Edn, Jephcott, A., (*R*) 583

A Manual of Anaesthesia for Emergency Surgery, 1st Edn, Donegan, J. H., (editor), (*R*) 350

Acupuncture Treatment and Anaesthesia, 4th Edn, Salim, M., (editor), (*R*) 702

An Introduction to Anaesthesiology, Coetzee, A., *et al.*, (editors), (*R*) 471

Anaesthesia for Thoracic Procedures, Marshall, B. E., *et al.*, (editors), (*R*) 473

Anaesthesia Review 5, Kaufman, L., (editor), (*R*) 118

Anatomy for Anaesthetists, Ellis, H., *et al.*, (editors), (*R*) 473

Anesthesia and Co-Existing Disease, 2nd Edn, Stoelting, R. K., *et al.*, (editors), (*R*) 471–472

Annual Review of Pulmonary and Critical Care Medicine 88/89, Matthay, R. A., *et al.*, (editors), (*R*) 116

Anyone Can Intubate, Whitten, C. E., (*R*) 583

Automation in Anesthesia—A Relief? Meijler, A. P., (*R*) 350

Care of the Critically Ill, 3rd Edn, Ayres, S. M., *et al.*, (editors), (*R*) 117

Clinical Anatomy for Anesthesiologists, Snell, R. S., *et al.*, (editors), (*R*) 702

Current Practice in Anesthesiology, 1st Edn, Rogers, M., (editor), (*R*) 584

Diamorphine: Its Chemistry, Pharmacology and Clinical Use, Scott, D. B., (editor), (*R*) 117

Imaging and Labelling Techniques in the Critically Ill, Kox, W., *et al.*, (editors), (*R*) 701

Intensive Care—Pocket Reference, Park, G. R., *et al.*, (editors), (*R*) 116

I.v. Anaesthesia, 2nd Edn, Dundee, J. W., *et al.*, (*R*) 238

Introduction to Anaesthesia: The Principles of Safe Practice, 7th Edn, Dripps, R. D., *et al.*, (*R*) 116–117

Medicine for Disasters, 1st Edn, Baskett, P., *et al.*, (editors), (*R*) 117–118

Neonatal Anaesthesia, 1st Edn, Cook, D. R., *et al.*, (editors), (*R*) 472–473

Obstetric Anesthesia · The Complicated Patient, 2nd Edn, James, F. M. III, *et al.*, (editors), (*R*) 582

Perspectives in Critical Care Medicine, Cerra, F. B., (editor), (*R*) 583–584

Pocket Manual of Anesthesia, 1st Edn, Lenz, G., *et al.*, (editors), (*R*) 701–702

Positioning the Surgical Patient, Anderton, J. M., *et al.*, (*R*) 238

Principles of Airway Management, 1st Edn, Finucane, B. T., *et al.*, (editors), (*R*) 116

Pulmonary Function Indices in Critical Care Patients, 1st Edn, Brunner, J. X., *et al.*, (*R*) 351

Recent Advances in Critical Care Medicine, Volume 3. Ledingham, I. McA., (editor), (*R*) 118–119

Surgery for Anaesthetists, Zorab, J. S. M., (editor), (*R*) 471

Understanding Anaesthesia, 2nd Edn, Carrie, L. E. S., *et al.*, (*R*) 472

Yearbook of Critical Care Medicine, 1988, 6th Edn, Rogers, M. C., (editor), (*R*) 582

Bradycardia, Effects of pipecuronium and pancuronium on the isolated rabbit heart, Deam, R. K., *et al.* 287–289

——, Haemodynamic effects of vecuronium, Wierda, J. M. K. H., *et al.* 194–198

Brain, Effect of general anaesthesia on the magnetic resonance imaging signal from the brain, Whitfield, A., *et al.* 694–696

Breathing systems, Comparison of the Magill and Lack anaesthetic breathing systems in anaesthetized patients, Millar, S. W., *et al.* 153–158

——, Controlled ventilation with a Mapleson A (Magill) breathing system: reassessment using a lung model, Tyler, C. K. G., *et al.* 462–466

——, Preliminary evaluation of the Enclosed Magill Breathing System, Bruce, W. C., *et al.* 144–149

——, Resistance to airflow in anaesthetic breathing systems, Martin, D. G., *et al.* 456–461

Buccal administration, Pharmacokinetics of morphine following administration by the buccal route, Manara, A. R., *et al.* 498–502

Bunsen solubility coefficient, Solubility of Freon-22 in blood and lung tissue, Franks, P. J., *et al.* 425–428

Bupivacaine, Alkalinization of bupivacaine for sciatic nerve blockade, Coventry, D. M., *et al.*, (*ARS*) 227P

——, Comparison of continuous paravertebral and extradural infusions of bupivacaine for pain relief after thoracotomy, Matthews, P. J., *et al.* 204–205

——, Continuous thoracic extradural 0.5% bupivacaine with or without morphine: effect on quality of blockade, lung function and the surgical stress response, Scott, N. B., *et al.* 253–257

——, Controlled trial of extradural bupivacaine with fentanyl, morphine or placebo for pain relief in labour, Lirzin, J. D., *et al.* 641–644

——, Does pretreatment with cimetidine and ranitidine affect the disposition of bupivacaine? Flynn, R. J., *et al.* 87–91

——, Effect of time and adrenaline on the feto-maternal distribution of bupivacaine, Reynolds, F., *et al.* 509–514

——, Effects of bupivacaine on inward currents and contraction in single myocytes isolated from guineapig ventricle, Victory, J. G. G., *et al.*, (*ARS*) 227–228P

——, Evaluation of a bupivacaine–morphine mixture for caudal analgesia in children, Wolf, A. R., *et al.*, (*ARS*) 221–222P

——, Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy, Drenger, B., *et al.* 82–86

——, Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy, Drenger, B., (*C*) 580

——, Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy, Lim, M., (*C*) 579

Bupivacaine, Extradural pressure following the injection of two volumes of bupivacaine, Paul, D. L., *et al.* 368–372
——, Low-dose intrathecal diamorphine analgesia following major orthopaedic surgery, Reay, B. A., *et al.* 248–252
——, Maternal and neonatal bupivacaine concentrations after spinal and extradural anaesthesia for Caesarean section, Jani, K., *et al.*, (*ARS*) 226–227P
——, Plain bupivacaine: 0.5% or 0.25% for spinal analgesia? Nielsen, T. H., *et al.* 164–167
——, Safety and efficacy of a low volume extradural test dose of bupivacaine in labour, Prince, G. D., *et al.* 503–508
——, Spinal anaesthesia with bupivacaine, Mitchell, R. W. D., *et al.*, (*C*) 113
——, Spinal anaesthesia with bupivacaine, Stienstra, R., *et al.*, (*C*) 112–113
——, Spread of spinal anaesthesia with plain 0.5% bupivacaine: influence of the vertebral interspace used for injection, Tuominen, M., *et al.* 358–361
Bupivacaine–morphine mixture, Evaluation of a bupivacaine–morphine mixture for caudal analgesia in children, Wolf, A. R., *et al.*, (*ARS*) 221–222P
BW B1090U, mivacurium chloride, Comparison of mivacurium and suxamethonium administered by bolus and infusion, Brandom, B. W., *et al.* 488–493

Caesarean section, Anaesthetic management for Caesarean section in a patient with uncorrected truncus arteriosus, Wilton, N. C. T., *et al.* 434–438
——, Awareness following different techniques of general anaesthesia for Caesarean section, Baraka, A., *et al.* 645–648
——, Comparison of 1.5% enflurane with 1.25% isoflurane in oxygen for Caesarean section: avoidance of awareness without nitrous oxide, Tunstall, M. E., *et al.* 138–143
——, Complications of spinal anaesthesia following extradural block for Caesarean section, Stone, P. A., *et al.* 335–337
——, Does pretreatment with cimetidine and ranitidine affect the disposition of bupivacaine? Flynn, R. J., *et al.* 87–91
——, Effect of time and adrenaline on the feto–maternal distribution of bupivacaine, Reynolds, F., *et al.* 509–514
——, Influence of preoperative gastric aspiration on the volume and pH of gastric contents in obstetric patients undergoing Caesarean section, Brock-Utne, J. G., *et al.* 397–401
——, Maternal and neonatal bupivacaine concentrations after spinal and extradural anaesthesia for Caesarean section, Jani, K., *et al.*, (*ARS*) 226–227P
——, Neurobehavioural effects of propofol on the neonate following elective Caesarean section, Celleno, D., *et al.* 649–654
——, Serial peak expiratory flow rates in mothers during Caesarean section under extradural anaesthesia, Gamil, M. 415–418
Caffeine, Effect of diltiazem and dantrolene on the contractility of isolated malignant hyperpyrexia-susceptible porcine skeletal muscle, Foster, P. S., *et al.* 566–572
——, Inhalation anaesthetics decrease calcium content of cardiac sarcoplasmic reticulum, Katsuoka, M., *et al.* 669–673
Calcium channel antagonist, Effect of diltiazem and dantrolene on the contractility of isolated malignant hyperpyrexia-susceptible porcine skeletal muscle, Foster, P. S., *et al.* 566–572
——, Effect of diltiazem on porcine malignant hyperpyrexia induced by suxamethonium and halothane, Foster, P. S., *et al.* 560–565
Calcium channel block, Effect of nicardipine infusion on the release of glutathione S-transferase following halothane anaesthesia, Ray, D. C., *et al.* 553–559
Calcium content, Inhalation anaesthetics decrease calcium content of cardiac sarcoplasmic reticulum, Katsuoka, M., *et al.* 669–673
Captopril, Cerebral blood flow during anaesthesia: influence of pretreatment with metoprolol or captopril, Jensen, K., *et al.* 321–323
Carbon dioxide, Effect of nalbuphine hydrochloride on the ventilatory and occlusion pressure responses to carbon dioxide in volunteers, Pugh, G. C., *et al.* 601–609
——, Oxygen consumption and carbon dioxide elimination in infants and children during anaesthesia and surgery, Lindahl, S. G. E. 70–76
Cardiac sarcoplasmic reticulum, Inhalation anaesthetics decrease calcium content of cardiac sarcoplasmic reticulum, Katsuoka, M., *et al.* 669–673
Cardiac surgery, Effect of ketanserin on sodium nitroprusside requirements, arterial pressure control and heart rate following coronary artery bypass surgery, Hodsman, N. B. A., *et al.* 527–531
Cardiovascular action, Hypotensive agents: an animal model, Bagshaw, R. J., (*C*) 112
——, Hypotensive agents: an animal model, Sury, M. R. J., *et al.*, (*C*) 112
Cardiovascular effects, Air embolism during total hip replacement: comparison of two surgical techniques, Evans, R. D., *et al.* 243–247
——, Alfentanil obtunds the cardiovascular and sympathoadrenal responses to suxamethonium-facilitated laryngoscopy and intubation, Scheinin, B., *et al.* 385–392
——, Cardiovascular and respiratory effects of ketorolac and alfentanil during anaesthesia, Brockway, M. S., *et al.*, (*ARS*) 224–225P
——, Effect of atracurium and laudanosine on the release of ^{3}H-noradrenaline, Kinjo, M., *et al.* 683–690
——, Glycopyrronium requirements for antagonism of the muscarinic side effects of edrophonium, Dodd, P., *et al.* 77–81
——, Neuromuscular and cardiovascular effects of doxacurium in children anaesthetized with halothane, Goudsouzian, N. G., *et al.* 263–268
Care of the Critically Ill, 3rd Edn, Ayres, S. M., *et al.*, (editors), (*R*) 117
Carotid body chemoreceptors, Effect of halothane, enflurane and isoflurane on carotid body chemoreceptor activity in the rabbit and the cat, Ponte, J., *et al.* 33–40
——, Effect of thiopentone, etomidate and propofol on carotid body chemoreceptor activity in the rabbit and the cat, Ponte, J., *et al.* 41–45
Cat, Effect of halothane, enflurane and isoflurane on carotid body chemoreceptor activity in the rabbit and the cat, Ponte, J., *et al.* 33–40
——, Effect of thiopentone, etomidate and propofol on carotid body chemoreceptor activity in the rabbit and the cat, Ponte, J., *et al.* 41–45
——, Pharmacokinetics and disposition of Org 9616 and Org 9426 in the cat, Khuenl-Brady, K. S., *et al.*, (*ARS*) 225–226P
Catecholamines, Plasma concentrations of catecholamines following intraocular irrigation with adrenaline, Fell, D., *et al.* 573–575
——, Use of magnesium sulphate in the anaesthetic management of phaeochromocytoma: a review of 17 anaesthetics, James, M. F. M. 616–623
Caudal anaesthesia, Evaluation of a bupivacaine–morphine mixture for caudal analgesia in children, Wolf, A. R., *et al.*, (*ARS*) 221–222P
Cement insertion, Air embolism during total hip

replacement: comparison of two surgical techniques, Evans, R. D., *et al.* 243–247

Cerebral blood flow (CBF), Cerebral blood flow during anaesthesia: influence of pretreatment with metoprolol or captopril, Jensen, K., *et al.* 321–323

Children, Antagonism of vecuronium with neostigmine in children: influence of the associated halogenated agent, Meistelman, C., *et al.*, (*ARS*) 228–229P

——, Changes in oxygen saturation during inhalation induction of anaesthesia in children, Sampaio, M. M., *et al.* 199–201

——, Comparison of total ventilatory compliance in sedated and anaesthetized infants and young children, Stack, C. G., *et al.*, (*ARS*) 232P

——, Effect of surface electrode positioning on the compound action potential evoked by ulnar nerve stimulation in anaesthetized infants and children, Kalli, I. 188–193

——, Estimation of Pa_{CO_2} from end-tidal P_{CO_2} and Hb saturation in cyanotic children, Fletcher, R., (*ARS*) 231P

——, Evaluation of a bupivacaine–morphine mixture for caudal analgesia in children, Wolf, A. R., *et al.*, (*ARS*) 221–222P

——, Is there a relationship between masseteric muscle spasm and malignant hyperpyrexia? Christian, A. S., *et al.* 540–544

——, Lung function in the supine and lateral decubitus positions in anaesthetized infants and children, Larsson, A., *et al.* 378–384

——, Neuromuscular and cardiovascular effects of doxacurium in children anaesthetized with halothane, Goudsouzian, N. G., *et al.* 263–268

——, Oxygen consumption and carbon dioxide elimination in infants and children during anaesthesia and surgery, Lindahl, S. G. E. 70–76

——, Significance of preload on mechanomyographic relaxometry in infants, children and adults, Leuwer, M., (*ARS*) 228P

Chloroform, Decay in blood chloroform concentrations after anaesthesia, Ordman, A. J., *et al.*, (*ARS*) 229P

Cholesterol, Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations, Gottardis, M., *et al.* 393–396

Chronotropic effects, Effects of pipecuronium and pancuronium on the isolated rabbit heart, Deam, R. K., *et al.* 287–289

Cimetidine, Does pretreatment with cimetidine and ranitidine affect the disposition of bupivacaine? Flynn, R. J., *et al.* 87–91

Cirrhosis, Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis, Parker, C. J. R., *et al.* 177–183

Cisapride, Cisapride and anaesthesia, Rowbotham, D. J., (*E*) 121–123

——, Effects on the lower oesophageal sphincter of cisapride given before the combined administration of atropine and neostigmine, Jones, M. J., *et al.* 124–128

Clinical Anatomy for Anesthesiologists, Snell, R. S., *et al.*, (editors), (*R*) 702

Closed-loop feedback, Closed-loop feedback control of propofol anaesthesia by quantitative EEG analysis in humans, Schwilden, H., *et al.* 290–296

Coeliac plexus block, Percutaneous anterior approach to the coeliac plexus using ultrasound, Montero Matamala, A., *et al.* 637–640

Complications, Complications of spinal anaesthesia following extradural block for Caesarean section, Stone, P. A., *et al.* 335–337

——, Perioperative complications following the use of vancomycin in children: a report of two cases, Best, C. J., *et al.* 576–577

Computerized infusion system, Computer controlled infusion of propofol, Tackley, R. M., *et al.* 46–53

Congenital cardiac disease, Anaesthetic management for Caesarean section in a patient with uncorrected truncus arteriosus, Wilton, N. C. T., *et al.* 434–438

——, Estimation of Pa_{CO_2} from end-tidal P_{CO_2} and Hb saturation in cyanotic children, Fletcher, R., (*ARS*) 231P

——, Relationship between alveolar deadspace and arterial oxygenation in children with congenital cardiac disease, Fletcher, R. 168–176

Continuous infusions, Comparison of continuous paravertebral and extradural infusions of bupivacaine for pain relief after thoracotomy, Matthews, P. J., *et al.* 204–205

Continuous positive airways pressure (CPAP), Evaluation of the Ambu CPAP system, Venn, P. J. H. 340–347

Controlled i.v. infusion, Blood:CSF glycine concentration gradient following a controlled i.v. infusion in dogs, Claffey, L. P., *et al.*, (*ARS*) 234–235P

Controlled ventilation, Comparison of the Bain and the ADE systems during controlled ventilation in adults, Shah, N. K., *et al.* 150–152

——, Controlled ventilation with a Mapleson A (Magill) breathing system: reassessment using a lung model, Tyler, C. K. G., *et al.* 462–466

Convulsions, Retrospective study of early postoperative convulsions after intracranial surgery with isoflurane or enflurane anaesthesia, Christys, A. R., *et al.* 624–627

Core temperature, Estimation of core temperature by use of an insulated arm, Keeler, J. F., *et al.*, (*ARS*) 223–224P

Cortical auditory evoked response, Early cortical auditory evoked response in anaesthesia: comparison of the effects of nitrous oxide and isoflurane, Newton, D. E. F., *et al.* 61–65

Cough suppression, Serial peak expiratory flow rates in mothers during Caesarean section under extradural anaesthesia, Gamil, M. 415–418

CSF, Blood:CSF glycine concentration gradient following a controlled i.v. infusion in dogs, Claffey, L. P., *et al.*, (*ARS*) 234–235P

Current Practice in Anesthesiology, 1st Edn, Rogers, M., (editor), (*R*) 584

Cyanotic children, Estimation of Pa_{CO_2} from end-tidal P_{CO_2} and Hb saturation in cyanotic children, Fletcher, R., (*ARS*) 231P

Cyanotic heart disease, Relationship between alveolar deadspace and arterial oxygenation in children with congenital cardiac disease, Fletcher, R. 168–176

Dantrolene, Effect of diltiazem and dantrolene on the contractility of isolated malignant hyperpyrexia-susceptible porcine skeletal muscle, Foster, P. S., *et al.* 566–572

Datex Relaxograph, Comparison of the Elwell Neuromuscular Indicator and the Datex Relaxograph, Canning, J., *et al.*, (*ARS*) 226P

——, Effect of suxamethonium given during recovery from atracurium, Black, A. M. S., (*C*) 348–349

Daycase surgery, Factors affecting headache following anaesthesia for urological daycase surgery, Faithfull, N. S., (*ARS*) 220–221P

Dental anaesthesia, Incidence of arrhythmias in dental anaesthesia: a cross-over comparison of halothane and isoflurane, Hutchison, G. L., *et al.* 518–521

Dextrose dilution, Effect of diluting propofol on the incidence of pain on injection and venous sequelae, Stokes, D. N., *et al.* 202–203

Diamorphine, Low-dose intrathecal diamorphine analgesia following major orthopaedic surgery, Reay, B. A., *et al.* 248–252

Diamorphine: Its Chemistry, Pharmacology and Clinical Use, Scott, D. B., (editor), (*R*) 117

Diaphragm, Neuromuscular block in diaphragm and hand, Derrington, M. C., (*C*) 236

——, Neuromuscular block in diaphragm and hand, Waud, B. E., (*C*) 236

Diaphragm–phrenic nerve preparation, *In vitro* investigation of the priming principle for rapid neuromuscular block, Storella, R. J., *et al.* 478–482

Diazepam, Effect of oral midazolam and diazepam on some pulmonary function tests, Fassoulaki, A., *et al.*, (*ARS*) 232P

Diclofenac sodium (Voltarol), Venous sequelae following i.v. administration of diclofenac, Campbell, W. I., *et al.* 545–547

Difficult intubation, Predicting difficult intubation, Bellhouse, C. P., *et al.*, (*C*) 469

——, Predicting difficult intubation, Wilson, M. E., *et al.*, (*C*) 469

——, Transilluminated tracheal intubation, Ainsworth, Q. P., *et al.* 494–497

——, X-ray laryngoscopy in patients with a history of difficult laryngoscopy during pregnancy, Fahy, L., *et al.*, (*ARS*) 234P

Diltiazem, Effect of diltiazem and dantrolene on the contractility of isolated malignant hyperpyrexia-susceptible porcine skeletal muscle, Foster, P. S , *et al.* 566–572

——, Effect of diltiazem on porcine malignant hyperpyrexia induced by suxamethonium and halothane, Foster, P. S., *et al.* 560–565

Disposition, Pharmacokinetics and disposition of Org 9616 and Org 9426 in the cat, Khuenl-Brady, K. S., *et al.*, (*ARS*) 225–226P

Dobutamine, Effect of dobutamine infusion on the adrenocortical response to halothane anaesthesia in ponies, Taylor, P M., (*ARS*) 219P

Dog, Blood:CSF glycine concentration gradient following a controlled i.v. infusion in dogs, Claffey, L. P., *et al.*, (*ARS*) 234–235P

——, Effects of propofol on pulmonary and systemic arterial pressure–flow relationships in hyperoxic and hypoxic dogs, Naeije, R., *et al.* 532–539

——, Neuromuscular block in diaphragm and hand, Derrington, M. C., (*C*) 236

——, Neuromuscular block in diaphragm and hand, Waud, B. E., (*C*) 236

Doppler ultrasonography, Air embolism during total hip replacement: comparison of two surgical techniques, Evans, R. D., *et al.* 243–247

Dose, Pharmacokinetics of alfentanil during and after a fixed rate infusion, van Beem, H., *et al.* 610–615

Double burst stimulation (DBS), Double burst stimulation (DBS): a new pattern of nerve stimulation to identify residual neuromuscular block, Engbæk, J., *et al.* 274–278

Doxacurium chloride, Doxacurium chloride: a preliminary clinical trial, Scott, R. P. F., *et al.* 373–377

——, Neuromuscular and cardiovascular effects of doxacurium in children anaesthetized with halothane, Goudsouzian, N. G., *et al.* 263–268

Doxapram, Doxapram and the neuromuscular junction, Pollard, B. J., *et al.* 664–668

——, Effect of oral doxapram on morphine-induced changes in the ventilatory response to carbon dioxide, Randall, N. P. C., *et al.* 159–163

Drug interactions, Perioperative complications following the use of vancomycin in children: a report of two cases, Best, C. J., *et al.* 576–577

Drug safety, The safety of new drugs, Hull, C. J., (*E*) 587–589

Edrophonium, Doxacurium chloride: a preliminary clinical trial, Scott, R. P. F., *et al.* 373–377

——, Glycopyrronium requirements for antagonism of the muscarinic side effects of edrophonium, Dodd, P., *et al.* 77–81

EEG analysis, Closed-loop feedback control of propofol anaesthesia by quantitative EEG analysis in humans, Schwilden, H., *et al.* 290–296

Eicosanoids, Effects of propofol on pulmonary and systemic arterial pressure–flow relationships in hyperoxic and hypoxic dogs, Naeije, R., *et al.* 532–539

Elderly patients, Bilateral pneumothorax following tracheal intubation, Biswas, C., *et al.* 338–339

——, Comparison of increase in end-tidal concentrations of halothane and isoflurane in elderly patients, Dwyer, R., *et al.*, (*ARS*) 219–220P

Electroacupuncture, Electroacupuncture and postoperative pain, Christensen, P. A., *et al.* 258–262

Electroencephalogram, Electroencephalographic effects of laudanosine in an animal model of epilepsy, Tateishi, A., *et al.* 548–552

Electromyography, Antagonism of moderate degrees of vecuronium-induced neuromuscular block by small doses of neostigmine, Johnson, R. A., *et al.* 483–487

——, Effect of surface electrode positioning on the compound action potential evoked by ulnar nerve stimulation in anaesthetized infants and children, Kalli, I. 188–193

——, Effect of suxamethonium given during recovery from atracurium, Scott, R. P. F., *et al.*, (*C*) 349

——, Train-of-four fade during onset and recovery of neuromuscular block: a study in non-anaesthetized subjects, Turner, G A., *et al.* 279–286

Elwell Neuromuscular Indicator, Comparison of the Elwell Neuromuscular Indicator and the Datex Relaxograph, Canning, J., *et al* , (*ARS*) 226P

EMLA (Eutectic Mixture of Local Anaesthetics), Anaesthesia of the skin, Colby, S., (*E*) 4–5

——, *In vivo* assessment of percutaneous local anaesthetic preparations, McCafferty, D. F., *et al.* 17–21

Enclosed Magill Breathing System, Preliminary evaluation of the Enclosed Magill Breathing System, Bruce, W. C., *et al.* 144–149

End-tidal carbon dioxide, Oxygen consumption and carbon dioxide elimination in infants and children during anaesthesia and surgery, Lindahl, S. G. E. 70–76

——, Relationship between alveolar deadspace and arterial oxygenation in children with congenital cardiac disease, Fletcher, R. 168–176

End-tidal concentrations, Comparison of increase in end-tidal concentrations of halothane and isoflurane in elderly patients, Dwyer, R., *et al.*, (*ARS*) 219–220P

End-tidal $P\text{CO}_2$, Estimation of Pa_{CO_2} from end-tidal $P\text{CO}_2$ and Hb saturation in cyanotic children, Fletcher, R , (*ARS*) 231P

Enflurane, Comparison of 1.5% enflurane with 1 25% isoflurane in oxygen for Caesarean section. avoidance of awareness without nitrous oxide, Tunstall, M. E., *et al.* 138–143

——, Effect of halothane, enflurane and isoflurane on body temperature during and after surgery, Ramachandra, V., *et al.* 409–414

——, Effect of halothane, enflurane and isoflurane on carotid body chemoreceptor activity in the rabbit and the cat, Ponte, J., *et al* 33–40

——, Effects of halothane, isoflurane and enflurane anaesthesia on the total ventilatory impedance of ponies, Young, S., (*ARS*) 230–231P

——, Inhalation anaesthetics decrease calcium content of cardiac sarcoplasmic reticulum, Katsuoka, M., *et al.* 669–673

——, Pretreatment with paracetamol inhibits metabolism of enflurane in rats, Hanna, A. N., *et al* 429–433

——, Retrospective study of early postoperative convulsions

after intracranial surgery with isoflurane or enflurane anaesthesia, Christys, A. R., *et al.* 624–627
Epilepsy, Electroencephalographic effects of laudanosine in an animal model of epilepsy, Tateishi, A., *et al.* 548–552
Etomidate, Effect of anaesthetic agents on bile flow and biliary excretion of ^{131}I-cholylglycyltyrosine in the rat, Mills, C. O., *et al.* 311–315
——, Effect of thiopentone, etomidate and propofol on carotid body chemoreceptor activity in the rabbit and the cat, Ponte, J., *et al.* 41–45
Evoked compound action potential (ECAP), Effect of surface electrode positioning on the compound action potential evoked by ulnar nerve stimulation in anaesthetized infants and children, Kalli, I. 188–193
Exeter cement gun, Air embolism during total hip replacement: comparison of two surgical techniques, Evans, R. D., *et al.* 243–247
Extracorporeal carbon dioxide removal (ECCO$_2$R), Hyperventilation haemolysis: are humans at risk? Dorrington, K. L., *et al.*, (*ARS*) 235P
Extracorporeal shock wave lithotripsy (ESWL), Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy, Drenger, B., *et al.* 82–86
——, Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy, Drenger, B., (*C*) 580
——, Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy, Lim, M., (*C*) 579
Extradural analgesia, Comparison of continuous paravertebral and extradural infusions of bupivacaine for pain relief after thoracotomy, Matthews, P. J., *et al.* 204–205
——, Complications of spinal anaesthesia following extradural block for Caesarean section, Stone, P. A., *et al.* 335–337
——, Continuous thoracic extradural 0.5% bupivacaine with or without morphine: effect on quality of blockade, lung function and the surgical stress response, Scott, N. B., *et al.* 253–257
——, Controlled trial of extradural bupivacaine with fentanyl, morphine or placebo for pain relief in labour, Lirzin, J. D., *et al.* 641–644
——, Does pretreatment with cimetidine and ranitidine affect the disposition of bupivacaine? Flynn, R. J., *et al.* 87–91
——, Effect of time and adrenaline on the feto–maternal distribution of bupivacaine, Reynolds, F., *et al.* 509–514
——, Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy, Drenger, B., *et al.* 82–86
——, Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy, Drenger, B., (*C*) 580
——, Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy, Lim, M., (*C*) 579
——, Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, Scott, D. B., (*C*) 578
——, Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, Scott, D. B., (*C*) 579
——, Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, Sosis, A., (*C*) 578
——, Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, Thorburn, J., (*C*) 578–579
——, Maternal and neonatal bupivacaine concentrations after spinal and extradural anaesthesia for Caesarean section, Jani, K., *et al.*, (*ARS*) 226–227P
——, Oxygen desaturation following sedation for regional analgesia, Smith, D. C., *et al.* 206–209
——, Safety and efficacy of a low volume extradural test dose of bupivacaine in labour, Prince, G. D., *et al.* 503–508
——, Serial peak expiratory flow rates in mothers during Caesarean section under extradural anaesthesia, Gamil, M. 415–418
Extradural bupivacaine, Continuous thoracic extradural 0.5% bupivacaine with or without morphine: effect on quality of blockade, lung function and the surgical stress response, Scott, N. B., *et al.* 253–257
Extradural pressure, Extradural pressure following the injection of two volumes of bupivacaine, Paul, D. L., *et al.* 368–372
Extradural space, Effects of halothane on electrically stimulated motor evoked potential in the extradural space, Loughnan, B. A., *et al.*, (*ARS*) 223P
——, Effects of halothane on somatosensory evoked potentials recorded in the extradural space, Loughnan, B. A., *et al.* 297–300
Eye surgery, Plasma concentrations of catecholamines following intraocular irrigation with adrenaline, Fell, D., *et al.* 573–575

Facioscapulohumeral muscular dystrophy, Anaesthetic management of a patient with facioscapulohumeral muscular dystrophy, Dresner, D L., *et al.* 331–334
Femoral nerve, Evaluation of "3 in 1" lumbar plexus block in patients having muscle biopsy, Madej, T. H., *et al.* 515–517
Fentanyl, Antroduodenal motility, pH and gastric emptying during balanced anaesthesia: comparison of pethidine and fentanyl, Schurizek, B. A., *et al.* 674–682
——, Controlled trial of extradural bupivacaine with fentanyl, morphine or placebo for pain relief in labour, Lirzin, J. D., *et al* 641–644
——, Effects of fentanyl and alfentanil on the change in intraocular pressure produced by suxamethonium and tracheal intubation, Sweeney, J., *et al.*, (*ARS*) 222P
——, GABA involvement in spinal analgesia with midazolam, Edwards, M., *et al.*, (*ARS*) 233P
——, Naloxone antagonizes the spinal analgesic effects of midazolam, Serrao, J. M., *et al.*, (*ARS*) 233–234P
Fetus, Effect of time and adrenaline on the feto–maternal distribution of bupivacaine, Reynolds, F., *et al.* 509–514
Fibreoptic intubation, Awake fibreoptic intubation of the patient at high risk of aspiration, Ovassapian, A., *et al.* 13–16
——, Teaching fibreoptic intubation, Forbes, R., *et al.*, (*C*) 113–114
Flumazenil, Naloxone antagonizes the spinal analgesic effects of midazolam, Serrao, J. M., *et al*, (*ARS*) 233–234P
Freon-22 solubility, Solubility of Freon-22 in blood and lung tissue, Franks, P. J., *et al.* 425–428
Fresh gas flow, Comparison of the Bain and the ADE systems during controlled ventilation in adults, Shah, N. K., *et al.* 150–152
Fresh gas flow rates, Comparison of the Magill and Lack anaesthetic breathing systems in anaesthetized patients, Millar, S. W., *et al* 153–158
Functional residual capacity, Lung function in the supine and lateral decubitus positions in anaesthetized infants and children, Larsson, A., *et al.* 378–384

GABA, GABA involvement in spinal analgesia with midazolam, Edwards, M., *et al.*, (*ARS*) 233P
Gas exchange, Oxygen consumption and carbon dioxide

elimination in infants and children during anaesthesia and surgery, Lindahl, S. G. E. 70–76
Gas exchange, Relationship between alveolar deadspace and arterial oxygenation in children with congenital cardiac disease, Fletcher, R. 168–176
Gastric dilatation, Acute gastric dilatation in an incarcerated hiatus hernia, Hopkins, C. S., *et al.* 108–111
Gastric emptying, Antroduodenal motility, pH and gastric emptying during balanced anaesthesia: comparison of pethidine and fentanyl, Schurizek, B. A., *et al.* 674–682
——, Cisapride and anaesthesia, Rowbotham, D. J , (*E*) 121–123
——, Effects of general anaesthesia with halothane on antroduodenal motility, pH and gastric emptying rate in man, Schurizek, B. A., *et al.* 129–137
Gastric pH, Antroduodenal motility, pH and gastric emptying during balanced anaesthesia: comparison of pethidine and fentanyl, Schurizek, B. A., *et al.* 674–682
——, Effects of general anaesthesia with halothane on antroduodenal motility, pH and gastric emptying rate in man, Schurizek, B. A., *et al.* 129–137
Gastrointestinal endoscopy, Haemodynamic and oxgen saturation changes during upper gastrointestinal endoscopy: evaluation of propofol and midazolam sedation, Patterson, K. W., *et al.*, (*ARS*) 222–223P
General anaesthesia, Awareness following different techniques of general anaesthesia for Caesarean section, Baraka, A., *et al.* 645–648
——, Effect of general anaesthesia on the magnetic resonance imaging signal from the brain, Whitfield, A., *et al.* 694–696
——, General anaesthetic modification of synaptic facilitation and long-term potentiation in hippocampus, MacIver, M. B., *et al.* 301–310
——, Neurobehavioural effects of propofol on the neonate following elective Caesarean section, Celleno, D., *et al.* 649–654
——, Studies on morphine disposition: influence of general anaesthesia on plasma concentrations of morphine and its metabolites, Sear, J. W., *et al.* 22–27
Glutathione S-transferase, Effect of nicardipine infusion on the release of glutathione S-transferase following halothane anaesthesia, Ray, D. C., *et al.* 553–559
Glycine, Blood:CSF glycine concentration gradient following a controlled i.v. infusion in dogs, Claffey, L. P., *et al.*, (*ARS*) 234–235P
Glycopyrronium, Glycopyrronium requirements for antagonism of the muscarinic side effects of edrophonium, Dodd, P., *et al.* 77–81
Greyhound, Hypotensive agents: an animal model, Bagshaw, R. J., (*C*) 112
——, Hypotensive agents: an animal model, Sury, M. R. J., *et al.*, (*C*) 112
Guineapig heart, Effects of bupivacaine on inward currents and contraction in single myocytes isolated from guineapig ventricle, Victory, J. G. G., *et al.*, (*ARS*) 227–228P
Guineapig right atrium preparation, Effect of atracurium and laudanosine on the release of ^{3}H-noradrenaline, Kinjo, M., *et al.* 683–690

H_2 blockers, Does pretreatment with cimetidine and ranitidine affect the disposition of bupivacaine? Flynn, R. J., *et al.* 87–91
Haemodynamic effects, Haemodynamic and oxgen saturation changes during upper gastrointestinal endoscopy: evaluation of propofol and midazolam sedation, Patterson, K. W., *et al.*, (*ARS*) 222–223P
——, Haemodynamic effects of vecuronium, Wierda, J. M. K. H., *et al.* 194–198
Haemoglobin saturation, Estimation of Pa_{CO_2} from end-tidal $P\text{CO}_2$ and Hb saturation in cyanotic children, Fletcher, R., (*ARS*) 231P
Halothane, Antagonism of vecuronium with neostigmine in children: influence of the associated halogenated agent, Meistelman, C., *et al.*, (*ARS*) 228–229P
——, Awareness following different techniques of general anaesthesia for Caesarean section, Baraka, A , *et al.* 645–648
——, Changes in oxygen saturation during inhalation induction of anaesthesia in children, Sampaio, M. M., *et al.* 199–201
——, Comparison of increase in end-tidal concentrations of halothane and isoflurane in elderly patients, Dwyer, R., *et al.*, (*ARS*) 219–220P
——, Effect of diltiazem and dantrolene on the contractility of isolated malignant hyperpyrexia-susceptible porcine skeletal muscle, Foster, P. S., *et al.* 566–572
——, Effect of diltiazem on porcine malignant hyperpyrexia induced by suxamethonium and halothane, Foster, P S., *et al.* 560–565
——, Effect of dobutamine infusion on the adrenocortical response to halothane anaesthesia in ponies, Taylor, P. M., (*ARS*) 219P
——, Effect of halothane, enflurane and isoflurane on body temperature during and after surgery, Ramachandra, V., *et al.* 409–414
——, Effect of halothane, enflurane and isoflurane on carotid body chemoreceptor activity in the rabbit and the cat, Ponte, J., *et al.* 33–40
——, Effect of nicardipine infusion on the release of glutathione S-transferase following halothane anaesthesia, Ray, D. C., *et al.* 553–559
——, Effects of general anaesthesia with halothane on antroduodenal motility, pH and gastric emptying rate in man, Schurizek, B. A., *et al.* 129–137
——, Effects of halothane, isoflurane and enflurane anaesthesia on the total ventilatory impedance of ponies, Young, S., (*ARS*) 230–231P
——, Effects of halothane on electrically stimulated motor evoked potential in the extradural space, Loughnan, B. A., *et al.*, (*ARS*) 223P
——, Effects of halothane on somatosensory evoked potentials recorded in the extradural space, Loughnan, B. A., *et al.* 297–300
——, General anaesthetic modification of synaptic facilitation and long-term potentiation in hippocampus, MacIver, M. B., *et al.* 301–310
——, Haemodynamic effects of vecuronium, Wierda, J M. K. H., *et al* 194–198
——, Incidence of arrhythmias in dental anaesthesia: a cross-over comparison of halothane and isoflurane, Hutchison, G. L., *et al.* 518–521
——, Inhalation anaesthetics decrease calcium content of cardiac sarcoplasmic reticulum, Katsuoka, M., *et al* 669–673
——, Oxygen consumption and carbon dioxide elimination in infants and children during anaesthesia and surgery, Lindahl, S. G. E. 70–76
Hand muscle, Neuromuscular block in diaphragm and hand, Derrington, M. C., (*C*) 236
——, Neuromuscular block in diaphragm and hand, Waud, B E , (*C*) 236
HDL-cholesterol, Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations, Gottardis, M., *et al.* 393–396
Head injuries, Nasotracheal intubation, paranasal sinusitis and head injuries, Fassoulaki, A., (*C*) 236
——, Nasotracheal intubation, paranasal sinusitis and head injuries, Hansen, M., *et al.*, (*C*) 237
Head surgery, Arterial oxygenation after different types of major head and neck surgery, Campbell, I. T., *et al.*, (*ARS*) 231–232P

Headache, Factors affecting headache following anaesthesia for urological daycase surgery, FAITHFULL, N. S., (*ARS*) 220–221P

Heart, Effects of pipecuronium and pancuronium on the isolated rabbit heart, DEAM, R. K., *et al.* 287–289

Heart block, Heart block following propofol: a case report, JAMES, M. F. M., *et al.* 213–215

Heart rate, Effect of ketanserin on sodium nitroprusside requirements, arterial pressure control and heart rate following coronary artery bypass surgery, HODSMAN, N. B. A., *et al.* 527–531

——, Neuromuscular and cardiovascular effects of doxacurium in children anaesthetized with halothane, GOUDSOUZIAN, N. G., *et al.* 263–268

Hepatic cirrhosis, Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis, PARKER, C. J. R., *et al.* 177–183

Hepatobiliary function, Effect of anaesthetic agents on bile flow and biliary excretion of ^{131}I-cholylglycyltyrosine in the rat, MILLS, C. O., *et al.* 311–315

Hepatotoxicity, Effect of nicardipine infusion on the release of glutathione S-transferase following halothane anaesthesia, RAY, D. C., *et al.* 553–559

——, Pretreatment with paracetamol inhibits metabolism of enflurane in rats, HANNA, A. N., *et al.* 429–433

Hiatus hernia, Acute gastric dilatation in an incarcerated hiatus hernia, HOPKINS, C. S., *et al.* 108–111

High frequency chest wall oscillation (HFCWO), High frequency ventilation, SYKES, M. K., (*E*) 475–477

High frequency jet ventilation, High frequency ventilation, SYKES, M. K., (*E*) 475–477

High frequency oscillation, Comparison of the effects of high frequency oscillation and controlled mechanical ventilation on hyaline membrane formation in a rabbit model of the neonatal respiratory distress syndrome, NIBLETT, D. J., *et al.* 628–636

——, High frequency ventilation, SYKES, M. K., (*E*) 475–477

High frequency positive pressure ventilation (HFPPV), High frequency ventilation, SYKES, M. K., (*E*) 475–477

High frequency ventilation, High frequency ventilation, SYKES, M. K., (*E*) 475–477

High thoracic extradural anaesthesia, Effect of high thoracic extradural anaesthesia on ventilatory response to hypercapnia in normal volunteers, KOCHI, T., *et al.* 362–367

Hip replacement, Air embolism during total hip replacement: comparison of two surgical techniques, EVANS, R. D., *et al.* 243–247

Hippocampal slice, General anaesthetic modification of synaptic facilitation and long-term potentiation in hippocampus, MACIVER, M. B., *et al.* 301–310

Hyaline membrane formation, Comparison of the effects of high frequency oscillation and controlled mechanical ventilation on hyaline membrane formation in a rabbit model of the neonatal respiratory distress syndrome, NIBLETT, D. J., *et al.* 628–636

Hypercapnic ventilatory response (HVR), Effect of high thoracic extradural anaesthesia on ventilatory response to hypercapnia in normal volunteers, KOCHI, T., *et al.* 362–367

Hypertension, Blood–brain barrier to pertechnetate following drug-induced hypotension, COOK, P. R., *et al.* 402–408

——, Effect of ketanserin on sodium nitroprusside requirements, arterial pressure control and heart rate following coronary artery bypass surgery, HODSMAN, N. B. A., *et al.* 527–531

Hyperthermia, Adrenal cortical reserve in patients undergoing muscle biopsy for malignant hyperthermia screening, FAIRBRASS, M J., *et al.* 66–69

Hyperventilation haemolysis, Hyperventilation haemolysis: are humans at risk? DORRINGTON, K. L., *et al*, (*ARS*) 235P

Hypotension, Blood–brain barrier to pertechnetate following drug-induced hypotension, COOK, P. R., *et al.* 402–408

——, Perioperative complications following the use of vancomycin in children: a report of two cases, BEST, C. J., *et al.* 576–577

Hypotensive agents, Hypotensive agents: an animal model, BAGSHAW, R. J., (*C*) 112

——, Hypotensive agents: an animal model, SURY, M. R. J., *et al.*, (*C*) 112

Hypoxaemia, Profound intraoperative atelectasis, SAMUELS, S. I., *et al.* 216–218

Hypoxaemia detection, Comparison of pulse oximeters: effects of vasoconstriction and venous engorgement, WILKINS, C. J., *et al.* 439–444

Hypoxia, Effect of halothane, enflurane and isoflurane on carotid body chemoreceptor activity in the rabbit and the cat, PONTE, J., *et al.* 33–40

——, Effect of thiopentone, etomidate and propofol on carotid body chemoreceptor activity in the rabbit and the cat, PONTE, J., *et al.* 41–45

——, Maternal oxygenation during normal labour, REED, P. N., *et al.* 316–318

——, Oxygen desaturation following sedation for regional analgesia, SMITH, D. C., *et al.* 206–209

Hypoxic pulmonary vasoconstriction, Effects of propofol on pulmonary and systemic arterial pressure–flow relationships in hyperoxic and hypoxic dogs, NAEIJE, R., *et al.* 532–539

^{131}I-cholylglycyltyrosine, Effect of anaesthetic agents on bile flow and biliary excretion of ^{131}I-cholylglycyltyrosine in the rat, MILLS, C. O., *et al.* 311–315

IEMG, Comparison of mechanomyography and integrated electromyography for monitoring suxamethonium block, BELL, P. F., *et al.*, (*ARS*) 225P

Imaging and Labelling Techniques in the Critically Ill, KOX, W., *et al.*, (editors), (*R*) 701

Induction dose, Influence of alcohol consumption on the induction dose of thiopentone, DUNDEE, J. W., *et al.*, (*ARS*) 229–230P

Infants, Comparison of total ventilatory compliance in sedated and anaesthetized infants and young children, STACK, C. G., *et al.*, (*ARS*) 232P

——, Effect of surface electrode positioning on the compound action potential evoked by ulnar nerve stimulation in anaesthetized infants and children, KALLI, I. 188–193

——, Is vecuronium a long-acting neuromuscular blocking agent in neonates and infants? MERETOJA, O. A. 184–187

——, Lung function in the supine and lateral decubitus positions in anaesthetized infants and children, LARSSON, A., *et al.* 378–384

——, Oxygen consumption and carbon dioxide elimination in infants and children during anaesthesia and surgery, LINDAHL, S. G. E. 70–76

——, Significance of preload on mechanomyographic relaxometry in infants, children and adults, LEUWER, M., (*ARS*) 228P

Infusion, Comparison of mivacurium and suxamethonium administered by bolus and infusion, BRANDOM, B. W., *et al.* 488–493

——, Computer controlled infusion of propofol, TACKLEY, R. M., *et al.* 46–53

——, Recovery of neuromuscular function after infusion or intermittent bolus doses of atracurium or vecuronium, GORDON, K. L., *et al.* 269–273

——, Use of continuous prolonged administration of atracurium in the ITU to a patient with myasthenia gravis, Pollard, B. J., *et al.* 95–97

Inhalation anaesthetic, General anaesthetic modification of synaptic facilitation and long-term potentiation in hippocampus, MacIver, M. B., *et al.* 301–310

——, Inhalation anaesthetics decrease calcium content of cardiac sarcoplasmic reticulum, Katsuoka, M., *et al.* 669–673

——, Pharmacokinetics of alfentanil during and after a fixed rate infusion, van Beem, H., *et al.* 610–615

Injection pain, Effect of diluting propofol on the incidence of pain on injection and venous sequelae, Stokes, D. N., *et al.* 202–203

Inotropic effects, Effects of pipecuronium and pancuronium on the isolated rabbit heart, Deam, R. K., *et al.* 287–289

Insulated arm, Estimation of core temperature by use of an insulated arm, Keeler, J. F., *et al.*, (*ARS*) 223–224P

Integrated electromyography, Comparison of mechanomyography and integrated electromyography for monitoring suxamethonium block, Bell, P. F., *et al.*, (*ARS*) 225P

Intensive Care—Pocket Reference, Park, G. R., *et al.*, (editors), (*R*) 116

Intensive Care Unit, Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations, Gottardis, M., *et al.* 393–396

——, Use of continuous prolonged administration of atracurium in the ITU to a patient with myasthenia gravis, Pollard, B. J., *et al.* 95–97

Interdigestive motility complex, Effects of general anaesthesia with halothane on antroduodenal motility, pH and gastric emptying rate in man, Schurizek, B. A., *et al.* 129–137

Intra-arterial injection, A new therapeutic approach to accidental intra-arterial injection of thiopentone, Vangerven, M., *et al.* 98–100

Intracranial surgery, Retrospective study of early postoperative convulsions after intracranial surgery with isoflurane or enflurane anaesthesia, Christys, A. R., *et al.* 624–627

Intraocular pressure, Effects of fentanyl and alfentanil on the change in intraocular pressure produced by suxamethonium and tracheal intubation, Sweeney, J., *et al.*, (*ARS*) 222P

Intraoperative atelectasis, Profound intraoperative atelectasis, Samuels, S. I., *et al.* 216–218

Intraoperative hypoxaemia, Profound intraoperative atelectasis, Samuels, S. I., *et al.* 216–218

Intraoperative monitoring, Median nerve evoked potentials during propofol anaesthesia, Scheepstra, G. L., *et al.* 92–94

Intrathecal administration, Low-dose intrathecal diamorphine analgesia following major orthopaedic surgery, Reay, B. A., *et al.* 248–252

Introduction to Anaesthesia: The Principles of Safe Practice, 7th Edn, Dripps, R. D., *et al.*, (*R*) 116–117

Intubating conditions, Doxacurium chloride: a preliminary clinical trial, Scott, R. P. F., *et al.* 373–377

Intubation, Aid to intubation, Welsh, B. E., (*C*) 469–470

——, Airways revisited, Vaughan, R. S., (*E*) 1–3

——, Bilateral pneumothorax following tracheal intubation, Biswas, C., *et al.* 338–339

——, Defining a standard intubating position using "Angle Finder", Horton, W. A., *et al.* 6–12

——, Predicting difficult intubation, Bellhouse, C. P., *et al.*, (*C*) 469

——, Predicting difficult intubation, Wilson, M. E., *et al.*, (*C*) 469

——, Teaching fibreoptic intubation, Forbes, R., *et al.*, (*C*) 113–114

——, X-ray laryngoscopy in patients with a history of difficult laryngoscopy during pregnancy, Fahy, L., *et al.*, (*ARS*) 234P

Isoflurane, Antagonism of vecuronium with neostigmine in children: influence of the associated halogenated agent, Meistelman, C., *et al.*, (*ARS*) 228–229P

——, Changes in oxygen saturation during inhalation induction of anaesthesia in children, Sampaio, M. M., *et al.* 199–201

——, Comparison of 1.5% enflurane with 1.25% isoflurane in oxygen for Caesarean section: avoidance of awareness without nitrous oxide, Tunstall, M. E., *et al.* 138–143

——, Comparison of increase in end-tidal concentrations of halothane and isoflurane in elderly patients, Dwyer, R., *et al.*, (*ARS*) 219–220P

——, Early cortical auditory evoked response in anaesthesia: comparison of the effects of nitrous oxide and isoflurane, Newton, D. E. F., *et al.* 61–65

——, Effect of halothane, enflurane and isoflurane on body temperature during and after surgery, Ramachandra, V., *et al.* 409–414

——, Effect of halothane, enflurane and isoflurane on carotid body chemoreceptor activity in the rabbit and the cat, Ponte, J., *et al.* 33–40

——, Effects of halothane, isoflurane and enflurane anaesthesia on the total ventilatory impedance of ponies, Young, S., (*ARS*) 230–231P

——, Incidence of arrhythmias in dental anaesthesia: a cross-over comparison of halothane and isoflurane, Hutchison, G L., *et al* 518–521

——, Retrospective study of early postoperative convulsions after intracranial surgery with isoflurane or enflurane anaesthesia, Christys, A. R., *et al.* 624–627

I.v. anaesthesia, Heart block following propofol: a case report, James, M. F. M., *et al.* 213–215

——, Median nerve evoked potentials during propofol anaesthesia, Scheepstra, G. L., *et al.* 92–94

I.v. Anaesthesia, 2nd Edn, Dundee, J. W., *et al.*, (*R*) 238

I.v. anaesthetics, Auditory evoked potentials during propofol anaesthesia in man, Chassard, D., *et al.* 522–526

I.v. infusion, Pharmacokinetics of alfentanil during and after a fixed rate infusion, van Beem, H., *et al.* 610–615

Ketamine, Awareness following different techniques of general anaesthesia for Caesarean section, Baraka, A., *et al.* 645–648

——, Comparison of the effects of sedation with midazolam or ketamine on the airway muscles, Drummond, G. B., (*ARS*) 230P

——, Interaction of ketamine with atracurium, Toft, P., *et al.* 319–320

Ketanserin, Effect of ketanserin on sodium nitroprusside requirements, arterial pressure control and heart rate following coronary artery bypass surgery, Hodsman, N. B. A., *et al.* 527–531

Ketocyclazocine, GABA involvement in spinal analgesia with midazolam, Edwards, M., *et al.*, (*ARS*) 233P

——, Naloxone antagonizes the spinal analgesic effects of midazolam, Serrao, J. M., *et al.*, (*ARS*) 233–234P

Ketorolac, Cardiovascular and respiratory effects of ketorolac and alfentanil during anaesthesia, Brockway, M. S., *et al.*, (*ARS*) 224–225P

Labour, Controlled trial of extradural bupivacaine with fentanyl, morphine or placebo for pain relief in labour, Lirzin, J. D., *et al.* 641–644

——, Maternal oxygenation during normal labour, Reed, P. N., *et al.* 316–318

——, Safety and efficacy of a low volume extradural test dose of bupivacaine in labour, Prince, G. D., *et al.* 503–508

Lack breathing system, Comparison of the Magill and Lack anaesthetic breathing systems in anaesthetized patients, MILLAR, S W., *et al.* 153–158

Landouzy–Dejerine muscular dystrophy, Anaesthetic management of a patient with facioscapulohumeral muscular dystrophy, DRESNER, D. L., *et al.* 331–334

Laryngoscopy, Alfentanil obtunds the cardiovascular and sympathoadrenal responses to suxamethonium-facilitated laryngoscopy and intubation, SCHEININ, B., *et al.* 385–392

——, Defining a standard intubating position using "Angle Finder", HORTON, W. A., *et al.* 6–12

——, X-ray laryngoscopy in patients with a history of difficult laryngoscopy during pregnancy, FAHY, L., *et al.*, (*ARS*) 234P

Lateral cutaneous nerve of thigh, Evaluation of "3 in 1" lumbar plexus block in patients having muscle biopsy, MADEJ, T. H , *et al.* 515–517

Lateral position, Lung function in the supine and lateral decubitus positions in anaesthetized infants and children, LARSSON, A., *et al.* 378–384

Laudanosine, Effect of atracurium and laudanosine on the release of ³H-noradrenaline, KINJO, M., *et al.* 683–690

——, Electroencephalographic effects of laudanosine in an animal model of epilepsy, TATEISHI, A., *et al.* 548–552

——, Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis, PARKER, C. J. R., *et al.* 177–183

Lignocaine, Effect of high thoracic extradural anaesthesia on ventilatory response to hypercapnia in normal volunteers, KOCHI, T., *et al.* 362–367

Local anaesthesia, Comparison of continuous paravertebral and extradural infusions of bupivacaine for pain relief after thoracotomy, MATTHEWS, P. J , *et al.* 204–205

Local anaesthetics, Anaesthesia of the skin, COLEY, S., (*E*) 4–5

——, Controlled trial of extradural bupivacaine with fentanyl, morphine or placebo for pain relief in labour, LIRZIN, J. D., *et al.* 641–644

——, Evaluation of "3 in 1" lumbar plexus block in patients having muscle biopsy, MADEJ, T. H., *et al.* 515–517

——, Extradural pressure following the injection of two volumes of bupivacaine, PAUL, D. L., *et al.* 368–372

——, *In vivo* assessment of percutaneous local anaesthetic preparations, MCCAFFERTY, D. F., *et al.* 17–21

——, Spread of spinal anaesthesia with plain 0.5% bupivacaine: influence of the vertebral interspace used for injection, TUOMINEN, M., *et al.* 358–361

——, The blood lancet in regional anaesthesia, DE ANDRES, J. A., (*C*) 348

Long term infusion, Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations, GOTTARDIS, M., *et al.* 393–396

Long-term potentiation, General anaesthetic modification of synaptic facilitation and long-term potentiation in hippocampus, MACIVER, M. B., *et al.* 301–310

LOS pressure, Cisapride and anaesthesia, ROWBOTHAM, D. J., (*E*) 121–123

Low lumbar extradural injection, Extradural pressure following the injection of two volumes of bupivacaine, PAUL, D. L., *et al.* 368–372

Lower oesophageal sphincter, Cisapride and anaesthesia, ROWBOTHAM, D. J., (*E*) 121–123

——, Effects on the lower oesophageal sphincter of cisapride given before the combined administration of atropine and neostigmine, JONES, M. J., *et al.* 124–128

——, Prostaglandins and the lower oesophageal sphincter, JONES, M. J., *et al.*, (*C*) 581

——, Prostaglandins and the lower oesophageal sphincter, MAHONEY, A., (*C*) 581

"3 in 1" Lumbar plexus block, Evaluation of "3 in 1" lumbar plexus block in patients having muscle biopsy, MADEJ, T. H., *et al.* 515–517

Lung compliance, Lung function in the supine and lateral decubitus positions in anaesthetized infants and children, LARSSON, A , *et al.* 378–384

Lung function, Lung function in the supine and lateral decubitus positions in anaesthetized infants and children, LARSSON, A., *et al.* 378–384

Lung model, Controlled ventilation with a Mapleson A (Magill) breathing system: reassessment using a lung model, TYLER, C. K. G., *et al.* 462–466

Lung tissue, Solubility of Freon-22 in blood and lung tissue, FRANKS, P. J., *et al.* 425–428

Lung volume, Arterial oxygenation after different types of major head and neck surgery, CAMPBELL, I. T , *et al.*, (*ARS*) 231–232P

Magill breathing system, Comparison of the Magill and Lack anaesthetic breathing systems in anaesthetized patients, MILLAR, S. W., *et al* 153–158

Magnesium sulphate, Use of magnesium sulphate in the anaesthetic management of phaeochromocytoma: a review of 17 anaesthetics, JAMES, M. F. M. 616–623

Magnetic resonance imaging, Effect of general anaesthesia on the magnetic resonance imaging signal from the brain, WHITFIELD, A , *et al.* 694–696

Malignant hyperpyrexia, Is there a relationship between masseteric muscle spasm and malignant hyperpyrexia? CHRISTIAN, A. S , *et al.* 540–544

Malignant hyperpyrexia-susceptible porcine muscle, Effect of diltiazem and dantrolene on the contractility of isolated malignant hyperpyrexia-susceptible porcine skeletal muscle, FOSTER, P. S., *et al.* 566–572

Malignant hyperthermia, Adrenal cortical reserve in patients undergoing muscle biopsy for malignant hyperthermia screening, FAIRBRASS, M. J., *et al* 66–69

——, Effect of propofol on the malignant hyperthermia susceptible pig model, KRIVOSIC-HORBER, R., *et al.* 691–693

——, Suxamethonium and malignant hyperthermia, FLETCHER, J. E., *et al.*, (*C*) 468

——, Suxamethonium and malignant hyperthermia, NELSON, T E., (*C*) 468–469

Malignant hyperthermia susceptible pig model, Effect of propofol on the malignant hyperthermia susceptible pig model, KRIVOSIC-HORBER, R., *et al.* 691–693

Manometry, Effects of general anaesthesia with halothane on antroduodenal motility, pH and gastric emptying rate in man, SCHURIZEK, B. A., *et al.* 129–137

Mapleson A (Magill) breathing system, Comparison of the Magill and Lack anaesthetic breathing systems in anaesthetized patients, MILLAR, S. W., *et al.* 153–158

——, Controlled ventilation with a Mapleson A (Magill) breathing system: reassessment using a lung model, TYLER, C. K. G., *et al.* 462–466

Mass spectrometry, Oxygen consumption and carbon dioxide elimination in infants and children during anaesthesia and surgery, LINDAHL, S G. E. 70–76

Masseteric muscle spasm, Is there a relationship between masseteric muscle spasm and malignant hyperpyrexia? CHRISTIAN, A. S., *et al.* 540–544

Maternal bupivacaine, Maternal and neonatal bupivacaine concentrations after spinal and extradural anaesthesia for Caesarean section, JANI, K., *et al* , (*ARS*) 226–227P

Maternal–fetal exchange, Effect of time and adrenaline on the feto–maternal distribution of bupivacaine, REYNOLDS, F., *et al.* 509–514

Maternal hypoxia, Maternal oxygenation during normal labour, REED, P. N., *et al.* 316–318

Maternal oxygenation, Maternal oxygenation during normal labour, REED, P. N., *et al.* 316–318

Mechanical ventilation, Lung function in the supine and lateral decubitus positions in anaesthetized infants and children, LARSSON, A., *et al.* 378–384

Mechanomyographic relaxometry, Significance of preload on mechanomyographic relaxometry in infants, children and adults, LEUWER, M., (*ARS*) 228P

Mechanomyography, Comparison of mechanomyography and integrated electromyography for monitoring suxamethonium block, BELL, P. F., *et al.*, (*ARS*) 225P

——, Effect of suxamethonium given during recovery from atracurium, SCOTT, R. P. F., *et al.*, (*C*) 349

——, Train-of-four fade during onset and recovery of neuromuscular block: a study in non-anaesthetized subjects, TURNER, G. A., *et al.* 279–286

Medicine for Disasters, 1st Edn, BASKETT, P., *et al.*, (editors), (*R*) 117–118

Methadone, Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy, DRENGER, B., *et al.* 82–86

——, Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy, DRENGER, B., (*C*) 580

——, Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy, LIM, M., (*C*) 579

Methionine, Short term effect of nitrous oxide on methionine and S-adenosyl methionine concentrations, ROYSTON, B. D., *et al.* 419–424

Methohexitone, Closed-loop feedback control of propofol anaesthesia by quantitative EEG analysis in humans, SCHWILDEN, H., *et al.* 290–296

Methoxyflurane, General anaesthetic modification of synaptic facilitation and long-term potentiation in hippocampus, MACIVER, M. B., *et al.* 301–310

Metoprolol, Cerebral blood flow during anaesthesia: influence of pretreatment with metoprolol or captopril, JENSEN, K., *et al.* 321–323

Microprocessor-controlled anaesthetic machine, A new microprocessor-controlled anaesthetic machine, SYKES, M. K., *et al.* 445–455

Midazolam, Comparison of the effects of sedation with midazolam or ketamine on the airway muscles, DRUMMOND, G. B., (*ARS*) 230P

——, Effect of oral midazolam and diazepam on some pulmonary function tests, FASSOULAKI, A., *et al.*, (*ARS*) 232P

——, GABA involvement in spinal analgesia with midazolam, EDWARDS, M., *et al.*, (*ARS*) 233P

——, Haemodynamic and oxgen saturation changes during upper gastrointestinal endoscopy: evaluation of propofol and midazolam sedation, PATTERSON, K. W., *et al.*, (*ARS*) 222–223P

——, Naloxone antagonizes the spinal analgesic effects of midazolam, SERRAO, J. M., *et al.*, (*ARS*) 233–234P

Mivacurium, Comparison of mivacurium and suxamethonium administered by bolus and infusion, BRANDOM, B. W., *et al.* 488–493

MMG, Comparison of mechanomyography and integrated electromyography for monitoring suxamethonium block, BELL, P. F., *et al.*, (*ARS*) 225P

Monitoring, Auditory evoked potentials during propofol anaesthesia in man, CHASSARD, D., *et al.* 522–526

——, Comparison of pulse oximeters: effects of vasoconstriction and venous engorgement, WILKINS, C. J., *et al.* 439–444

——, Neuromuscular and cardiovascular effects of doxacurium in children anaesthetized with halothane, GOUDSOUZIAN, N. G., *et al.* 263–268

——, Pulse oximeters: essential monitors with limitations, KIDD, J. F., *et al.*, (*E*) 355–357

——, The anaesthetist's activities in the operating theatre, GOODMAN, N. W., (*C*) 700

——, The anaesthetist's activities in the operating theatre, MCDONALD, J. S., *et al.*, (*C*) 700

Morphine, Continuous thoracic extradural 0.5% bupivacaine with or without morphine: effect on quality of blockade, lung function and the surgical stress response, SCOTT, N. B., *et al.* 253–257

——, Controlled trial of extradural bupivacaine with fentanyl, morphine or placebo for pain relief in labour, LIRZIN, J. D., *et al.* 641–644

——, Effect of oral doxapram on morphine-induced changes in the ventilatory response to carbon dioxide, RANDALL, N. P. C., *et al.* 159–163

——, Evaluation of a bupivacaine–morphine mixture for caudal analgesia in children, WOLF, A. R., *et al.*, (*ARS*) 221–222P

——, Pharmacokinetics of morphine following administration by the buccal route, MANARA, A. R., *et al.* 498–502

——, Studies on morphine disposition: influence of general anaesthesia on plasma concentrations of morphine and its metabolites, SEAR, J. W., *et al.* 22–27

——, Studies on morphine disposition. influence of renal failure on the kinetics of morphine and its metabolites, SEAR, J. W., *et al.* 28–32

Morphine-3-glucuronide (M3G), Studies on morphine disposition. influence of general anaesthesia on plasma concentrations of morphine and its metabolites, SEAR, J. W., *et al.* 22–27

——, Studies on morphine disposition: influence of renal failure on the kinetics of morphine and its metabolites, SEAR, J. W., *et al.* 28–32

Morphine-6-glucuronide (M6G), Studies on morphine disposition: influence of general anaesthesia on plasma concentrations of morphine and its metabolites, SEAR, J. W., *et al.* 22–27

——, Studies on morphine disposition: influence of renal failure on the kinetics of morphine and its metabolites, SEAR, J. W., *et al.* 28–32

Motor evoked potential, Effects of halothane on electrically stimulated motor evoked potential in the extradural space, LOUGHNAN, B. A., *et al.*, (*ARS*) 223P

Muscular dystrophy, Anaesthetic management of a patient with facioscapulohumeral muscular dystrophy, DRESNER, D. L., *et al.* 331–334

Myasthenia gravis, Use of continuous prolonged administration of atracurium in the ITU to a patient with myasthenia gravis, POLLARD, B. J., *et al.* 95–97

Myocardial contractility, Effects of pipecuronium and pancuronium on the isolated rabbit heart, DEAM, R. K., *et al.* 287–289

Myocardial function, Effect of nitrous oxide during basal propofol anaesthesia on myocardium with normal and critically restricted blood supply, DIEDERICKS, J., *et al.*, (*ARS*) 224P

——, Effects of bupivacaine on inward currents and contraction in single myocytes isolated from guineapig ventricle, VICTORY, J. G. G., *et al.*, (*ARS*) 227–228P

Myocytes, Effects of bupivacaine on inward currents and contraction in single myocytes isolated from guineapig ventricle, VICTORY, J. G. G., *et al.*, (*ARS*) 227–228P

Myopathy, Is there a relationship between masseteric muscle spasm and malignant hyperpyrexia? CHRISTIAN, A. S., *et al.* 540–544

Nalbuphine, Effect of nalbuphine hydrochloride on the ventilatory and occlusion pressure responses to carbon dioxide in volunteers, PUGH, G. C., *et al.* 601–609

Naloxone, Effect of nalbuphine hydrochloride on the ventilatory and occlusion pressure responses to carbon dioxide in volunteers, PUGH, G. C., *et al.* 601–609

——, Naloxone antagonizes the spinal analgesic effects of midazolam, SERRAO, J. M., *et al.*, (*ARS*) 233–234P

Nasotracheal intubation, Nasotracheal intubation, paranasal sinusitis and head injuries, FASSOULAKI, A., (*C*) 236

——, Nasotracheal intubation, paranasal sinusitis and head injuries, Hansen, M., *et al.*, (*C*) 237
Natural killer cell activity, Natural killer cell activity in a patient undergoing resection of phaeochromocytoma, Tønnesen, E., *et al.* 327–330
Nausea, Low-dose intrathecal diamorphine analgesia following major orthopaedic surgery, Reay, B A., *et al.* 248–252
Neck surgery, Arterial oxygenation after different types of major head and neck surgery, Campbell, I. T., *et al.*, (*ARS*) 231–232P
Negative inotropic effect, Inhalation anaesthetics decrease calcium content of cardiac sarcoplasmic reticulum, Katsuoka, M., *et al.* 669–673
Neonatal Anaesthesia, 1st Edn, Cook, D. R., *et al.*, (editors), (*R*) 472–473
Neonatal bupivacaine, Maternal and neonatal bupivacaine concentrations after spinal and extradural anaesthesia for Caesarean section, Jani, K., *et al.*, (*ARS*) 226–227P
Neonatal neurobehavioural testing, Neurobehavioural effects of propofol on the neonate following elective Caesarean section, Celleno, D., *et al.* 649–654
Neonatal respiratory distress syndrome, Comparison of the effects of high frequency oscillation and controlled mechanical ventilation on hyaline membrane formation in a rabbit model of the neonatal respiratory distress syndrome, Niblett, D. J., *et al.* 628–636
Neonates, Is vecuronium a long-acting neuromuscular blocking agent in neonates and infants? Meretoja, O. A. 184–187
Neostigmine, Antagonism of moderate degrees of vecuronium-induced neuromuscular block by small doses of neostigmine, Johnson, R. A., *et al.* 483–487
——, Antagonism of vecuronium with neostigmine in children: influence of the associated halogenated agent, Meistelman, C., *et al.*, (*ARS*) 228–229P
——, Doxacurium chloride: a preliminary clinical trial, Scott, R. P. F., *et al.* 373–377
——, Effect of suxamethonium given during recovery from atracurium, Black, A. M. S., (*C*) 348–349
——, Effect of suxamethonium given during recovery from atracurium, Scott, R. P. F., *et al.*, (*C*) 349
——, Effects on the lower oesophageal sphincter of cisapride given before the combined administration of atropine and neostigmine, Jones, M. J., *et al.* 124–128
Nerve block, Alkalinization of bupivacaine for sciatic nerve blockade, Coventry, D. M., *et al.*, (*ARS*) 227P
Nerve stimulation, Double burst stimulation (DBS): a new pattern of nerve stimulation to identify residual neuromuscular block, Engbæk, J., *et al.* 274–278
Neurobehavioural effects, Neurobehavioural effects of propofol on the neonate following elective Caesarean section, Celleno, D., *et al.* 649–654
Neurogenic pulmonary oedema, Neurogenic pulmonary oedema precipitated by induction of anaesthesia, Braude, N., *et al.* 101–103
Neurolept anaesthesia, Haemodynamic effects of vecuronium, Wierda, J. M. K. H., *et al.* 194–198
Neuromuscular block, Accelerated recovery from combined atracurium–vecuronium neuromuscular block, Stirt, J. A. 697–699
——, Antagonism of moderate degrees of vecuronium-induced neuromuscular block by small doses of neostigmine, Johnson, R. A., *et al.* 483–487
——, Antagonism of vecuronium with neostigmine in children: influence of the associated halogenated agent, Meistelman, C., *et al.*, (*ARS*) 228–229P
——, Comparison of mechanomyography and integrated electromyography for monitoring suxamethonium block, Bell, P. F., *et al.*, (*ARS*) 225P
——, Comparison of mivacurium and suxamethonium administered by bolus and infusion, Brandom, B. W., *et al* 488–493
——, Dose–response curves for suxamethonium in neonates, infants and children, Meakin, G., *et al.* 655–658
——, Double burst stimulation (DBS): a new pattern of nerve stimulation to identify residual neuromuscular block, Engbæk, J., *et al* 274–278
——, Doxacurium chloride. a preliminary clinical trial, Scott, R. P. F., *et al.* 373–377
——, Effect of atracurium and laudanosine on the release of ^{3}H-noradrenaline, Kinjo, M., *et al.* 683–690
——, Effect of surface electrode positioning on the compound action potential evoked by ulnar nerve stimulation in anaesthetized infants and children, Kalli, I. 188–193
——, Effects of pipecuronium and pancuronium on the isolated rabbit heart, Deam, R. K , *et al.* 287–289
——, Electroencephalographic effects of laudanosine in an animal model of epilepsy, Tateishi, A., *et al.* 548–552
——, *In vitro* investigation of the priming principle for rapid neuromuscular block, Storella, R. J., *et al.* 478–482
——, Influence of suxamethonium on the action of subsequently administered vecuronium or pancuronium, Ono, K., *et al.* 324–326
——, Interaction of ketamine with atracurium, Toft, P., *et al.* 319–320
——, Is vecuronium a long-acting neuromuscular blocking agent in neonates and infants? Meretoja, O. A. 184–187
——, Neuromuscular and cardiovascular effects of doxacurium in children anaesthetized with halothane, Goudsouzian, N. G., *et al.* 263–268
——, Neuromuscular block in diaphragm and hand, Derrington, M. C., (*C*) 236
——, Neuromuscular block in diaphragm and hand, Waud, B. E., (*C*) 236
——, Parkinsonism and the anaesthetist, Ho, A. M.-H., (*C*) 580
——, Parkinsonism and the anaesthetist, Severn, A M., (*C*) 580–581
——, Pharmacokinetics and disposition of Org 9616 and Org 9426 in the cat, Khuenl-Brady, K. S., *et al.*, (*ARS*) 225–226P
——, Prolonged suxamethonium-induced neuromuscular block associated with organophosphate poisoning, Weeks, D. B., *et al.*, (*C*) 237
——, Recovery of neuromuscular function after infusion or intermittent bolus doses of atracurium or vecuronium, Gordon, K. L., *et al* 269–273
——, Train-of-four fade during onset and recovery of neuromuscular block: a study in non-anaesthetized subjects, Turner, G. A., *et al.* 279–286
——, Use of atracurium or vecuronium to prolong the action of tubocurarine, Middleton, C M., *et al* 659–663
——, Use of continuous prolonged administration of atracurium in the ITU to a patient with myasthenia gravis, Pollard, B. J., *et al.* 95–97
Neuromuscular junction, Doxapram and the neuromuscular junction, Pollard, B. J., *et al.* 664–668
Neuromuscular transmission, Double burst stimulation (DBS): a new pattern of nerve stimulation to identify residual neuromuscular block, Engbæk, J., *et al.* 274–278
——, Doxapram and the neuromuscular junction, Pollard, B. J., *et al.* 664–668
Neurostimulation, The blood lancet in regional anaesthesia, De Andres, J. A., (*C*) 348
New anaesthetic machine, A new microprocessor-controlled anaesthetic machine, Sykes, M. K., *et al.* 445–455
New drugs, The safety of new drugs, Hull, C. J., (*E*) 587–589
Nicardipine, Effect of nicardipine infusion on the release

of glutathione S-transferase following halothane anaesthesia, Ray, D. C., *et al.* 553–559

Nitrous oxide, Comparison of 1.5% enflurane with 1.25% isoflurane in oxygen for Caesarean section: avoidance of awareness without nitrous oxide, Tunstall, M. E., *et al.* 138–143

——, Early cortical auditory evoked response in anaesthesia: comparison of the effects of nitrous oxide and isoflurane, Newton, D. E. F., *et al.* 61–65

——, Effect of nitrous oxide during basal propofol anaesthesia on myocardium with normal and critically restricted blood supply, Diederickx, J., *et al.*, (*ARS*) 224P

——, Short term effect of nitrous oxide on methionine and S-adenosyl methionine concentrations, Royston, B. D., *et al.* 419–424

Non-steroidal anti-inflammatory drugs, Venous sequelae following i.v. administration of diclofenac, Campbell, W. I., *et al.* 545–547

^{3}H-Noradrenaline, Effect of atracurium and laudanosine on the release of ^{3}H-noradrenaline, Kinjo, M., *et al.* 683–690

Obstetric anaesthesia, Controlled trial of extradural bupivacaine with fentanyl, morphine or placebo for pain relief in labour, Lirzin, J. D., *et al.* 641–644

——, Dose–response curves for suxamethonium in neonates, infants and children, Meakin, G., *et al.* 655–658

——, Influence of preoperative gastric aspiration on the volume and pH of gastric contents in obstetric patients undergoing Caesarean section, Brock-Utne, J. G., *et al.* 397–401

——, Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, Scott, D. B., (*C*) 578

——, Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, Scott, D. B., (*C*) 579

——, Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, Sosis, A., (*C*) 578

——, Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, Thorburn, J., (*C*) 578–579

——, Neurobehavioural effects of propofol on the neonate following elective Caesarean section, Celleno, D., *et al.* 649–654

Obstetric Anesthesia · The Complicated Patient, 2nd Edn, James, F. M. III, *et al.*, (editors), (*R*) 582

Obturator nerve, Evaluation of "3 in 1" lumbar plexus block in patients having muscle biopsy, Madej, T. H., *et al.* 515–517

Occlusion pressure, Effect of nalbuphine hydrochloride on the ventilatory and occlusion pressure responses to carbon dioxide in volunteers, Pugh, G. C., *et al.* 601–609

Oesophageal balloon pressure, Measurement of transdiaphragmatic pressure, Derrington, M. C., (*C*) 238

——, Measurement of transdiaphragmatic pressure, Higgs, B., (*C*) 237–238

Opioid anaesthetics, Controlled trial of extradural bupivacaine with fentanyl, morphine or placebo for pain relief in labour, Lirzin, J. D., *et al.* 641–644

——, Naloxone antagonizes the spinal analgesic effects of midazolam, Serrao, J. M., *et al.*, (*ARS*) 233–234P

——, Pharmacokinetics of morphine following administration by the buccal route, Manara, A. R., *et al.* 498–502

Oral administration, Effect of oral doxapram on morphine-induced changes in the ventilatory response to carbon dioxide, Randall, N. P. C., *et al* 159–163

——, Effect of oral midazolam and diazepam on some pulmonary function tests, Fassoulaki, A., *et al.*, (*ARS*) 232P

Org 9426, Pharmacokinetics and disposition of Org 9616 and Org 9426 in the cat, Khuenl-Brady, K. S., *et al.*, (*ARS*) 225–226P

Org 9616, Pharmacokinetics and disposition of Org 9616 and Org 9426 in the cat, Khuenl-Brady, K. S., *et al.*, (*ARS*) 225–226P

Organophosphate poisoning, Prolonged suxamethonium-induced neuromuscular block associated with organophosphate poisoning, Weeks, D. B., *et al.*, (*C*) 237

Orogastric tube, Influence of preoperative gastric aspiration on the volume and pH of gastric contents in obstetric patients undergoing Caesarean section, Brock-Utne, J. G., *et al* 397–401

Orthopaedic surgery, Low-dose intrathecal diamorphine analgesia following major orthopaedic surgery, Reay, B. A., *et al.* 248–252

Ostwald solubility coefficient, Solubility of Freon-22 in blood and lung tissue, Franks, P. J., *et al.* 425–428

Oxygen consumption, Oxygen consumption and carbon dioxide elimination in infants and children during anaesthesia and surgery, Lindahl, S. G. E. 70–76

Oxygen monitoring, Oxygen desaturation following sedation for regional analgesia, Smith, D. C., *et al.* 206–209

Oxygen saturation, Changes in oxygen saturation during inhalation induction of anaesthesia in children, Sampaio, M. M., *et al.* 199–201

——, Haemodynamic and oxgen saturation changes during upper gastrointestinal endoscopy: evaluation of propofol and midazolam sedation, Patterson, K. W., *et al.*, (*ARS*) 222–223P

Pa_{CO_2}, Estimation of Pa_{CO_2} from end-tidal PCO$_2$ and Hb saturation in cyanotic children, Fletcher, R., (*ARS*) 231P

Paediatric anaesthesia, Anaesthesia of the skin, Coley, S., (*E*) 4–5

——, Dose–response curves for suxamethonium in neonates, infants and children, Meakin, G., *et al.* 655–658

——, Lung function in the supine and lateral decubitus positions in anaesthetized infants and children, Larsson, A., *et al.* 378–384

Pancuronium, Double burst stimulation (DBS): a new pattern of nerve stimulation to identify residual neuromuscular block, Engbæk, J., *et al.* 274–278

——, Effects of pipecuronium and pancuronium on the isolated rabbit heart, Deam, R. K., *et al.* 287–289

——, Influence of suxamethonium on the action of subsequently administered vecuronium or pancuronium, Ono, K., *et al.* 324–326

——, Pancuronium allergy: a case report, Patriarca, G., *et al.* 210–212

Paracetamol, Effects of general anaesthesia with halothane on antroduodenal motility, pH and gastric emptying rate in man, Schurizek, B. A., *et al.* 129–137

——, Pretreatment with paracetamol inhibits metabolism of enflurane in rats, Hanna, A. N., *et al.* 429–433

Paranasal sinusitis, Nasotracheal intubation, paranasal sinusitis and head injuries, Fassoulaki, A., (*C*) 236

——, Nasotracheal intubation, paranasal sinusitis and head injuries, Hansen, M., *et al.*, (*C*) 237

Paravertebral anaesthesia, Comparison of continuous paravertebral and extradural infusions of bupivacaine for pain relief after thoracotomy, Matthews, P. J., *et al.* 204–205

Parkinsonism, Parkinsonism and the anaesthetist, Ho, A. M.-H., (*C*) 580

——, Parkinsonism and the anaesthetist, Severn, A. M., (*C*) 580–581

Patient characteristics, Extradural pressure following the injection of two volumes of bupivacaine, PAUL, D. L., *et al.* 368–372

Patient controlled analgesia, Electroacupuncture and postoperative pain, CHRISTENSEN, P. A., *et al.* 258–262

$P\text{co}_2$, Estimation of Pa_{CO_2} from end-tidal $P\text{co}_2$ and Hb saturation in cyanotic children, FLETCHER, R., (*ARS*) 231P

Peak expiratory flow, Effect of oral midazolam and diazepam on some pulmonary function tests, FASSOULAKI, A., *et al.*, (*ARS*) 232P

——, Serial peak expiratory flow rates in mothers during Caesarean section under extradural anaesthesia, GAMIL, M. 415–418

Pentobarbitone, Effect of anaesthetic agents on bile flow and biliary excretion of ^{131}I-cholylglycyltyrosine in the rat, MILLS, C. O., *et al.* 311–315

Percutaneous anaesthesia, Anaesthesia of the skin, COLEY, S., (*E*) 4–5

——, *In vivo* assessment of percutaneous local anaesthetic preparations, MCCAFFERTY, D. F., *et al.* 17–21

Peripheral nerve stimulator, Effect of suxamethonium given during recovery from atracurium, SCOTT, R. P. F., *et al.*, (*C*) 349

Permeability, Blood–brain barrier to pertechnetate following drug-induced hypotension, COOK, P. R., *et al* 402–408

Perspectives in Critical Care Medicine, CERRA, F. B., (editor), (*R*) 583–584

Pertechnetate, Blood–brain barrier to pertechnetate following drug-induced hypotension, COOK, P. R., *et al.* 402–408

Pethidine, Antroduodenal motility, pH and gastric emptying during balanced anaesthesia: comparison of pethidine and fentanyl, SCHURIZEK, B. A., *et al.* 674–682

Phaeochromocytoma, Natural killer cell activity in a patient undergoing resection of phaeochromocytoma, TØNNESEN, E., *et al.* 327–330

——, Use of magnesium sulphate in the anaesthetic management of phaeochromocytoma: a review of 17 anaesthetics, JAMES, M. F. M. 616–623

Pharmacokinetics, *In vitro* investigation of the priming principle for rapid neuromuscular block, STORELLA, R. J., *et al.* 478–482

——, Pharmacokinetics and disposition of Org 9616 and Org 9426 in the cat, KHUENL-BRADY, K. S., *et al.*, (*ARS*) 225–226P

——, Pharmacokinetics of alfentanil during and after a fixed rate infusion, VAN BEEM, H., *et al.* 610–615

——, Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis, PARKER, C. J. R., *et al.* 177–183

——, Pharmacokinetics of morphine following administration by the buccal route, MANARA, A. R., *et al.* 498–502

——, Studies on morphine disposition: influence of renal failure on the kinetics of morphine and its metabolites, SEAR, J. W., *et al.* 28–32

Phrenic nerve–diaphragm preparation, *In vitro* investigation of the priming principle for rapid neuromuscular block, STORELLA, R. J., *et al.* 478–482

Pig, Teaching fibreoptic intubation, FORBES, R., *et al.*, (*C*) 113–114

Pig model, Effect of propofol on the malignant hyperthermia susceptible pig model, KRIVOSIC-HORBER, R., *et al.* 691–693

Pipecuronium, Effects of pipecuronium and pancuronium on the isolated rabbit heart, DEAM, R. K., *et al.* 287–289

Plain bupivacaine, Plain bupivacaine: 0.5% or 0.25% for spinal analgesia? NIELSEN, T. H., *et al.* 164–167

Plasma adrenaline, Plasma concentrations of catecholamines following intraocular irrigation with adrenaline, FELL, D., *et al.* 573–575

Plasma catecholamines, Natural killer cell activity in a patient undergoing resection of phaeochromocytoma, TØNNESEN, E., *et al.* 327–330

Plasma concentration, Studies on morphine disposition: influence of general anaesthesia on plasma concentrations of morphine and its metabolites, SEAR, J. W., *et al.* 22–27

Pleural pressure, Measurement of transdiaphragmatic pressure, DERRINGTON, M. C., (*C*) 238

——, Measurement of transdiaphragmatic pressure, HIGGS, B., (*C*) 237–238

Pocket Manual of Anesthesia, 1st Edn, LENZ, G., *et al.*, (editors), (*R*) 701–702

Ponies, Effect of dobutamine infusion on the adrenocortical response to halothane anaesthesia in ponies, TAYLOR, P. M., (*ARS*) 219P

——, Effects of halothane, isoflurane and enflurane anaesthesia on the total ventilatory impedance of ponies, YOUNG, S., (*ARS*) 230–231P

Porcine malignant hyperpyrexia syndrome, Effect of diltiazem on porcine malignant hyperpyrexia induced by suxamethonium and halothane, FOSTER, P. S., *et al.* 560–565

Porphyria, Use of propofol in a patient with porphyria, MCLOUGHLIN, C., (*C*) 114

Positioning the Surgical Patient, ANDERTON, J. M., *et al.*, (*R*) 238

Positive end-expiratory pressure, Comparison of the effects of high frequency oscillation and controlled mechanical ventilation on hyaline membrane formation in a rabbit model of the neonatal respiratory distress syndrome, NIBLETT, D. J., *et al.* 628–636

Postoperative pain, Continuous thoracic extradural 0.5% bupivacaine with or without morphine: effect on quality of blockade, lung function and the surgical stress response, SCOTT, N. B., *et al.* 253–257

——, Electroacupuncture and postoperative pain, CHRISTENSEN, P. A., *et al.* 258–262

Posture, Spinal anaesthesia with bupivacaine, MITCHELL, R. W. D., *et al.*, (*C*) 113

——, Spinal anaesthesia with bupivacaine, STIENSTRA, R., *et al.*, (*C*) 112–113

Potassium chloride, Effect of diltiazem and dantrolene on the contractility of isolated malignant hyperpyrexia-susceptible porcine skeletal muscle, FOSTER, P. S., *et al.* 566–572

Pregnancy, X-ray laryngoscopy in patients with a history of difficult laryngoscopy during pregnancy, FAHY, L., *et al.*, (*ARS*) 234P

Premedication, Pharmacokinetics of morphine following administration by the buccal route, MANARA, A. R., *et al.* 498–502

Preoperative gastric aspiration, Influence of preoperative gastric aspiration on the volume and pH of gastric contents in obstetric patients undergoing Caesarean section, BROCK-UTNE, J. G., *et al.* 397–401

Preoxygenation, Preoxygenation, GOLD, M. I., (*E*) 241

Priming principle, *In vitro* investigation of the priming principle for rapid neuromuscular block, STORELLA, R. J., *et al.* 478–482

Principles of Airway Management, 1st Edn, FINUCANE, B. T., *et al.*, (editors), (*R*) 116

Propofol, Auditory evoked potentials during propofol anaesthesia in man, CHASSARD, D., *et al.* 522–526

——, Closed-loop feedback control of propofol anaesthesia by quantitative EEG analysis in humans, SCHWILDEN, H., *et al.* 290–296

——, Computer controlled infusion of propofol, TACKLEY, R. M., *et al.* 46–53

——, Effect of anaesthetic agents on bile flow and biliary excretion of ^{131}I-cholylglycyltyrosine in the rat, MILLS, C. O., *et al.* 311–315

Propofol, Effect of diluting propofol on the incidence of pain on injection and venous sequelae, STOKES, D. N., *et al.* 202–203
——, Effect of nitrous oxide during basal propofol anaesthesia on myocardium with normal and critically restricted blood supply, DIEDERICKS, J., *et al.*, (*ARS*) 224P
——, Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations, GOTTARDIS, M., *et al.* 393–396
——, Effect of propofol on the malignant hyperthermia susceptible pig model, KRIVOSIC-HORBER, R., *et al.* 691–693
——, Effect of thiopentone, etomidate and propofol on carotid body chemoreceptor activity in the rabbit and the cat, PONTE, J., *et al.* 41–45
——, Effects of propofol on pulmonary and systemic arterial pressure–flow relationships in hyperoxic and hypoxic dogs, NAEIJE, R., *et al.* 532–539
——, Haemodynamic and oxgen saturation changes during upper gastrointestinal endoscopy: evaluation of propofol and midazolam sedation, PATTERSON, K. W., *et al.*, (*ARS*) 222–223P
——, Heart block following propofol: a case report, JAMES, M. F. M., *et al.* 213–215
——, Median nerve evoked potentials during propofol anaesthesia, SCHEEPSTRA, G. L., *et al.* 92–94
——, Neurobehavioural effects of propofol on the neonate following elective Caesarean section, CELLENO, D., *et al.* 649–654
——, Propofol for induction and maintenance of anaesthesia: comparison between younger and older patients, SCHEEPSTRA, G. L., *et al.* 54–60
——, Use of propofol in a patient with porphyria, MCLOUGHLIN, C., (*C*) 114
Prostaglandins, Prostaglandins and the lower oesophageal sphincter, JONES, M. J., *et al.*, (*C*) 581
——, Prostaglandins and the lower oesophageal sphincter, MAHONEY, A., (*C*) 581
Pulmonary function, Continuous thoracic extradural 0.5% bupivacaine with or without morphine: effect on quality of blockade, lung function and the surgical stress response, SCOTT, N. B., *et al* 253–257
——, Effect of oral midazolam and diazepam on some pulmonary function tests, FASSOULAKI, A., *et al.*, (*ARS*) 232P
Pulmonary Function Indices in Critical Care Patients, 1st Edn, BRUNNER, J. X., *et al.*, (*R*) 351
Pulmonary gas mixing, Lung function in the supine and lateral decubitus positions in anaesthetized infants and children, LARSSON, A., *et al.* 378–384
Pulmonary oedema, Neurogenic pulmonary oedema precipitated by induction of anaesthesia, BRAUDE, N., *et al.* 101–103
Pulse oximeters, Comparison of pulse oximeters: effects of vasoconstriction and venous engorgement, WILKINS, C. J., *et al.* 439–444
Pulse oximetry, Maternal oxygenation during normal labour, REED, P. N., *et al.* 316–318
——, Oxygen desaturation following sedation for regional analgesia, SMITH, D. C., *et al.* 206–209
——, Pulse oximeters: essential monitors with limitations, KIDD, J. F., *et al.*, (*E*) 355–357

Quantitative EEG analysis, Closed-loop feedback control of propofol anaesthesia by quantitative EEG analysis in humans, SCHWILDEN, H., *et al.* 290–296

Rabbit, Blood–brain barrier to pertechnetate following drug-induced hypotension, COOK, P. R., *et al.* 402–408
——, Comparison of the effects of high frequency oscillation and controlled mechanical ventilation on hyaline membrane formation in a rabbit model of the neonatal respiratory distress syndrome, NIBLETT, D J., *et al.* 628–636
——, Effect of halothane, enflurane and isoflurane on carotid body chemoreceptor activity in the rabbit and the cat, PONTE, J., *et al.* 33–40
——, Effect of thiopentone, etomidate and propofol on carotid body chemoreceptor activity in the rabbit and the cat, PONTE, J., *et al* 41–45
——, Effects of pipecuronium and pancuronium on the isolated rabbit heart, DEAM, R. K., *et al.* 287–289
Radioimmunoassay, Studies on morphine disposition: influence of renal failure on the kinetics of morphine and its metabolites, SEAR, J W, *et al.* 28–32
Ranitidine, Does pretreatment with cimetidine and ranitidine affect the disposition of bupivacaine? FLYNN, R. J., *et al.* 87–91
——, Influence of preoperative gastric aspiration on the volume and pH of gastric contents in obstetric patients undergoing Caesarean section, BROCK-UTNE, J. G., *et al.* 397–401
Rat, Effect of anaesthetic agents on bile flow and biliary excretion of ^{131}I-cholylglycyltyrosine in the rat, MILLS, C. O., *et al.* 311–315
——, *In vitro* investigation of the priming principle for rapid neuromuscular block, STORELLA, R. J., *et al* 478–482
——, Pretreatment with paracetamol inhibits metabolism of enflurane in rats, HANNA, A. N., *et al.* 429–433
Rat phrenic nerve–diaphragm preparation, Doxapram and the neuromuscular junction, POLLARD, B. J., *et al* 664–668
Rebreathing, Effect of high thoracic extradural anaesthesia on ventilatory response to hypercapnia in normal volunteers, KOCHI, T., *et al.* 362–367
Recall, Awareness following different techniques of general anaesthesia for Caesarean section, BARAKA, A., *et al.* 645–648
Recent Advances in Critical Care Medicine, Volume 3., LEDINGHAM, I MCA., (editor), (*R*) 118–119
Recovery Interest Group, The Recovery Interest Group, ROSEN, M., *et al*, (*C*) 470
Regional anaesthesia, Oxygen desaturation following sedation for regional analgesia, SMITH, D. C., *et al.* 206–209
——, The blood lancet in regional anaesthesia, DE ANDRES, J A., (*C*) 348
Regurgitation, Awake fibreoptic intubation of the patient at high risk of aspiration, OVASSAPIAN, A., *et al.* 13–16
Renal failure, Studies on morphine disposition: influence of renal failure on the kinetics of morphine and its metabolites, SEAR, J. W., *et al.* 28–32
Respiratory effects, Cardiovascular and respiratory effects of ketorolac and alfentanil during anaesthesia, BROCKWAY, M. S., *et al.*, (*ARS*) 224–225P
Respiratory inductive plethysomograph, Effect of high thoracic extradural anaesthesia on ventilatory response to hypercapnia in normal volunteers, KOCHI, T., *et al* 362–367
Rewarming, Effect of halothane, enflurane and isoflurane on body temperature during and after surgery, RAMACHANDRA, V., *et al.* 409–414
Rib cage, Effect of high thoracic extradural anaesthesia on ventilatory response to hypercapnia in normal volunteers, KOCHI, T., *et al.* 362–367
Right–left shunting, Relationship between alveolar deadspace and arterial oxygenation in children with congenital cardiac disease, FLETCHER, R. 168–176

S-adenosyl methionine, Short term effect of nitrous oxide on methionine and S-adenosyl methionine concentrations, ROYSTON, B. D., *et al.* 419–424
Safe practice, The anaesthetist's activities in the operating theatre, GOODMAN, N. W., (*C*) 700

——, The anaesthetist's activities in the operating theatre, McDonald, J. S., *et al.*, (*C*) 700

Safety of drugs, The safety of new drugs, Hull, C. J., (*E*) 587–589

Scholander apparatus, Solubility of Freon-22 in blood and lung tissue, Franks, P. J., *et al.* 425–428

Sciatic nerve block, Alkalinization of bupivacaine for sciatic nerve blockade, Coventry, D. M., *et al.*, (*ARS*) 227P

Screening, Effect of propofol on the malignant hyperthermia susceptible pig model, Krivosic-Horber, R., *et al.* 691–693

Sedation, Haemodynamic and oxgen saturation changes during upper gastrointestinal endoscopy: evaluation of propofol and midazolam sedation, Patterson, K. W., *et al.*, (*ARS*) 222–223P

Serum lipids, Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations, Gottardis, M., *et al.* 393–396

Short Synacthen Test (SST), Adrenal cortical reserve in patients undergoing muscle biopsy for malignant hyperthermia screening, Fairbrass, M. J., *et al.* 66–69

Sodium citrate, Influence of preoperative gastric aspiration on the volume and pH of gastric contents in obstetric patients undergoing Caesarean section, Brock-Utne, J. G., *et al.* 397–401

Sodium nitroprusside, Effect of ketanserin on sodium nitroprusside requirements, arterial pressure control and heart rate following coronary artery bypass surgery, Hodsman, N. B. A , *et al.* 527–531

Solubility, Solubility of Freon-22 in blood and lung tissue, Franks, P. J., *et al.* 425–428

Somatosensory evoked potentials (SEP), Effects of halothane on somatosensory evoked potentials recorded in the extradural space, Loughnan, B. A., *et al.* 297–300

——, Median nerve evoked potentials during propofol anaesthesia, Scheepstra, G. L., *et al.* 92–94

Spinal anaesthesia, Complications of spinal anaesthesia following extradural block for Caesarean section, Stone, P. A., *et al.* 335–337

——, GABA involvement in spinal analgesia with midazolam, Edwards, M., *et al.*, (*ARS*) 233P

——, Low-dose intrathecal diamorphine analgesia following major orthopaedic surgery, Reay, B. A., *et al.* 248–252

——, Maternal and neonatal bupivacaine concentrations after spinal and extradural anaesthesia for Caesarean section, Jani, K., *et al.*, (*ARS*) 226–227P

——, Naloxone antagonizes the spinal analgesic effects of midazolam, Serrao, J. M., *et al.*, (*ARS*) 233–234P

——, Oxygen desaturation following sedation for regional analgesia, Smith, D. C., *et al.* 206–209

——, Plain bupivacaine: 0 5% or 0.25% for spinal analgesia? Nielsen, T. H., *et al.* 164–167

——, Predicting the spread of spinal anaesthesia, Wildsmith, J. A. W , (*E*) 353–354

——, Spinal anaesthesia and surgical blood loss, Donald, J. R., (*C*) 114

——, Spinal anaesthesia and surgical blood loss, Smith, G., (*C*) 115

——, Spinal anaesthesia and surgical blood loss, Worsley, M. H., *et al.*, (*C*) 114

——, Spinal anaesthesia with bupivacaine, Mitchell, R. W. D., *et al.*, (*C*) 113

——, Spinal anaesthesia with bupivacaine, Stienstra, R., *et al.*, (*C*) 112–113

——, Spread of spinal anaesthesia with plain 0.5% bupivacaine: influence of the vertebral interspace used for injection, Tuominen, M., *et al.* 358–361

Spinal interspace, Spread of spinal anaesthesia with plain 0.5% bupivacaine: influence of the vertebral interspace used for injection, Tuominen, M., *et al.* 358–361

Spontaneous breathing, Lung function in the supine and lateral decubitus positions in anaesthetized infants and children, Larsson, A., *et al.* 378–384

——, Oxygen consumption and carbon dioxide elimination in infants and children during anaesthesia and surgery, Lindahl, S. G. E. 70–76

Sprague–Dawley rats, Pretreatment with paracetamol inhibits metabolism of enflurane in rats, Hanna, A N., *et al.* 429–433

Spread, Predicting the spread of spinal anaesthesia, Wildsmith, J. A. W., (*E*) 353–354

Stress response, Continuous thoracic extradural 0 5% bupivacaine with or without morphine: effect on quality of blockade, lung function and the surgical stress response, Scott, N. B., *et al* 253–257

Supine position, Lung function in the supine and lateral decubitus positions in anaesthetized infants and children, Larsson, A., *et al.* 378–384

Surgery for Anaesthetists, Zorab, J. S. M., (editor), (*R*) 471

Suxamethonium, Alfentanil obtunds the cardiovascular and sympathoadrenal responses to suxamethonium-facilitated laryngoscopy and intubation, Scheinin, B., *et al.* 385–392

——, Comparison of mechanomyography and integrated electromyography for monitoring suxamethonium block, Bell, P. F., *et al.*, (*ARS*) 225P

——, Comparison of mivacurium and suxamethonium administered by bolus and infusion, Brandom, B. W., *et al.* 488–493

——, Dose–response curves for suxamethonium in neonates, infants and children, Meakin, G., *et al* 655–658

——, Effect of diltiazem on porcine malignant hyperpyrexia induced by suxamethonium and halothane, Foster, P. S., *et al.* 560–565

——, Effect of suxamethonium given during recovery from atracurium, Black, A. M. S., (*C*) 348–349

——, Effect of suxamethonium given during recovery from atracurium, Scott, R. P. F., *et al.*, (*C*) 349

——, Effects of fentanyl and alfentanil on the change in intraocular pressure produced by suxamethonium and tracheal intubation, Sweeney, J., *et al.*, (*ARS*) 222P

——, Fatal haemopathological consequences of general anaesthesia, Wright, P. J., *et al.* 104–107

——, Influence of suxamethonium on the action of subsequently administered vecuronium or pancuronium, Ono, K., *et al.* 324–326

——, Prolonged suxamethonium-induced neuromuscular block associated with organophosphate poisoning, Weeks, D. B., *et al.*, (*C*) 237

——, Suxamethonium and malignant hyperthermia, Fletcher, J. E., *et al.*, (*C*) 468

——, Suxamethonium and malignant hyperthermia, Nelson, T. E., (*C*) 468–469

Synaptic facilitation, General anaesthetic modification of synaptic facilitation and long-term potentiation in hippocampus, MacIver, M. B., *et al.* 301–310

Test doses, Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, Scott, D. B., (*C*) 578

——, Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, Scott, D. B., (*C*) 579

——, Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, Sosis, A., (*C*) 578

——, Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia, Thorburn, J., (*C*) 578–579

——, Safety and efficacy of a low volume extradural test dose of bupivacaine in labour, Prince, G. D., *et al.* 503–508

Thiopentone, A new therapeutic approach to accidental intra-arterial injection of thiopentone, Vangerven, M., *et al.* 98–100

Thiopentone, Awareness following different techniques of general anaesthesia for Caesarean section, Baraka, A., *et al.* 645–648

——, Effect of thiopentone, etomidate and propofol on carotid body chemoreceptor activity in the rabbit and the cat, Ponte, J., *et al.* 41–45

——, Fatal haemopathological consequences of general anaesthesia, Wright, P. J., *et al.* 104–107

——, Influence of alcohol consumption on the induction dose of thiopentone, Dundee, J. W., *et al.*, (*ARS*) 229–230P

Thoractomy, Comparison of continuous paravertebral and extradural infusions of bupivacaine for pain relief after thoracotomy, Matthews, P. J., *et al.* 204–205

Tibialis anterior muscle, Neuromuscular block in diaphragm and hand, Derrington, M. C., (*C*) 236

——, Neuromuscular block in diaphragm and hand, Waud, B. E., (*C*) 236

Tidal volume, Oxygen consumption and carbon dioxide elimination in infants and children during anaesthesia and surgery, Lindahl, S. G. E. 70–76

Topical anaesthesia, Anaesthesia of the skin, Coley, S., (*E*) 4–5

——, *In vivo* assessment of percutaneous local anaesthetic preparations, McCafferty, D. F., *et al.* 17–21

Total anaesthesia, Propofol for induction and maintenance of anaesthesia: comparison between younger and older patients, Scheepstra, G. L., *et al.* 54–60

Total hip replacement, Air embolism during total hip replacement: comparison of two surgical techniques, Evans, R. D., *et al.* 243–247

Total ventilatory compliance, Comparison of total ventilatory compliance in sedated and anaesthetized infants and young children, Stack, C. G., *et al.*, (*ARS*) 232P

Toxicity, Neurobehavioural effects of propofol on the neonate following elective Caesarean section, Celleno, D., *et al.* 649–654

Tracheal intubation, Bilateral pneumothorax following tracheal intubation, Biswas, C., *et al.* 338–339

——, Effects of fentanyl and alfentanil on the change in intraocular pressure produced by suxamethonium and tracheal intubation, Sweeney, J., *et al.*, (*ARS*) 222P

——, Predicting difficult intubation, Bellhouse, C. P., *et al.*, (*C*) 469

——, Predicting difficult intubation, Wilson, M. E., *et al.*, (*C*) 469

——, Transilluminated tracheal intubation, Ainsworth, Q. P., *et al.* 494–497

Train-of-four, Antagonism of moderate degrees of vecuronium-induced neuromuscular block by small doses of neostigmine, Johnson, R. A., *et al.* 483–487

——, Comparison of the Elwell Neuromuscular Indicator and the Datex Relaxograph, Canning, J., *et al.*, (*ARS*) 226P

——, Double burst stimulation (DBS): a new pattern of nerve stimulation to identify residual neuromuscular block, Engbæk, J., *et al.* 274–278

——, Neuromuscular and cardiovascular effects of doxacurium in children anaesthetized with halothane, Goudsouzian, N. G., *et al.* 263–268

——, Train-of-four fade during onset and recovery of neuromuscular block: a study in non-anaesthetized subjects, Turner, G. A., *et al.* 279–286

Transdiaphragmatic pressure, Measurement of transdiaphragmatic pressure, Derrington, M. C., (*C*) 238

——, Measurement of transdiaphragmatic pressure, Higgs, B., (*C*) 237–238

Transillumination, Transilluminated tracheal intubation, Ainsworth, Q. P., *et al.* 494–497

Triglyceride, Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations, Gottardis, M., *et al.* 393–396

Truncus arteriosus, Anaesthetic management for Caesarean section in a patient with uncorrected truncus arteriosus, Wilton, N C. T., *et al.* 434–438

Tubocurarine, Use of atracurium or vecuronium to prolong the action of tubocurarine, Middleton, C. M., *et al.* 659–663

Ulnar nerve stimulation, Effect of surface electrode positioning on the compound action potential evoked by ulnar nerve stimulation in anaesthetized infants and children, Kalli, I. 188–193

Ultrasound, Percutaneous anterior approach to the coeliac plexus using ultrasound, Montero Matamala, A., *et al.* 637–640

Understanding Anaesthesia, 2nd Edn, Carrie, L. E. S., *et al.*, (*R*) 472

Upper gastrointestinal endoscopy, Haemodynamic and oxgen saturation changes during upper gastrointestinal endoscopy: evaluation of propofol and midazolam sedation, Patterson, K. W., *et al.*, (*ARS*) 222–223P

Urinary retention, Low-dose intrathecal diamorphine analgesia following major orthopaedic surgery, Reay, B. A., *et al.* 248–252

Urokinase, A new therapeutic approach to accidental intra-arterial injection of thiopentone, Vangerven, M., *et al.* 98–100

Urological surgery, Factors affecting headache following anaesthesia for urological daycase surgery, Faithfull, N. S., (*ARS*) 220–221P

Vancomycin, Perioperative complications following the use of vancomycin in children: a report of two cases, Best, C. J., *et al.* 576–577

Vascular pressure–flow relationships, Effects of propofol on pulmonary and systemic arterial pressure–flow relationships in hyperoxic and hypoxic dogs, Naeije, R., *et al.* 532–539

Vasoconstriction, Comparison of pulse oximeters: effects of vasoconstriction and venous engorgement, Wilkins, C. J., *et al.* 439–444

Vecuronium, Accelerated recovery from combined atracurium–vecuronium neuromuscular block, Stirt, J. A. 697–699

——, Antagonism of moderate degrees of vecuronium-induced neuromuscular block by small doses of neostigmine, Johnson, R. A., *et al.* 483–487

——, Antagonism of vecuronium with neostigmine in children: influence of the associated halogenated agent, Meistelman, C., *et al.*, (*ARS*) 228–229P

——, Atracurium—a post-marketing surveillance study: U.K. study and discussion, Lawson, D. H., *et al.* 596–600

——, Effects of pipecuronium and pancuronium on the isolated rabbit heart, Deam, R. K., *et al.* 287–289

——, Haemodynamic effects of vecuronium, Wierda, J. M. K. H., *et al.* 194–198

——, Influence of suxamethonium on the action of subsequently administered vecuronium or pancuronium, Ono, K., *et al.* 324–326

——, Is vecuronium a long-acting neuromuscular blocking agent in neonates and infants? Meretoja, O. A. 184–187

——, Recovery of neuromuscular function after infusion or intermittent bolus doses of atracurium or vecuronium, Gordon, K. L., *et al.* 269–273

——, Use of atracurium or vecuronium to prolong the action of tubocurarine, Middleton, C. M., *et al.* 659–663

Venous occlusion, Comparison of pulse oximeters: effects of vasoconstriction and venous engorgement, Wilkins, C. J., *et al.* 439–444

Venous sequelae, Effect of diluting propofol on the incidence of pain on injection and venous sequelae, Stokes, D. N., *et al.* 202–203
——, Venous sequelae following i.v. administration of diclofenac, Campbell, W. I., *et al.* 545–547
Ventilation, Comparison of total ventilatory compliance in sedated and anaesthetized infants and young children, Stack, C. G., *et al.*, (*ARS*) 232P
——, Effect of nalbuphine hydrochloride on the ventilatory and occlusion pressure responses to carbon dioxide in volunteers, Pugh, G. C., *et al.* 601–609
——, Effect of oral doxapram on morphine-induced changes in the ventilatory response to carbon dioxide, Randall, N. P. C., *et al.* 159–163
——, Effects of halothane, isoflurane and enflurane anaesthesia on the total ventilatory impedance of ponies, Young, S., (*ARS*) 230–231P
——, Preliminary evaluation of the Enclosed Magill Breathing System, Bruce, W. C., *et al.* 144–149
Vertebral interspace, Spread of spinal anaesthesia with plain 0.5% bupivacaine: influence of the vertebral interspace used for injection, Tuominen, M., *et al.* 358–361
Vital capacity, Effect of oral midazolam and diazepam on some pulmonary function tests, Fassoulaki, A., *et al.*, (*ARS*) 232P
Vitamin B_{12}, Short term effect of nitrous oxide on methionine and S-adenosyl methionine concentrations, Royston, B. D., *et al.* 419–424
Volatile anaesthetics, Changes in oxygen saturation during inhalation induction of anaesthesia in children, Sampaio, M. M., *et al.* 199–201
——, Comparison of 1.5% enflurane with 1.25% isoflurane in oxygen for Caesarean section: avoidance of awareness without nitrous oxide, Tunstall, M. E., *et al.* 138–143
——, Early cortical auditory evoked response in anaesthesia: comparison of the effects of nitrous oxide and isoflurane, Newton, D. E. F., *et al.* 61–65
——, Pretreatment with paracetamol inhibits metabolism of enflurane in rats, Hanna, A. N., *et al.* 429–433
Vomiting, Low-dose intrathecal diamorphine analgesia following major orthopaedic surgery, Reay, B. A., *et al.* 248–252

Weight, Pharmacokinetics of alfentanil during and after a fixed rate infusion, van Beem, H., *et al.* 610–615
Whole body protein, Whole body protein turnover during anaesthesia and surgery, Carli, F., *et al.*, (*ARS*) 220P
Winnie's technique, Evaluation of "3 in 1" lumbar plexus block in patients having muscle biopsy, Madej, T. H., *et al.* 515–517

X-ray laryngoscopy, X-ray laryngoscopy in patients with a history of difficult laryngoscopy during pregnancy, Fahy, L., *et al.*, (*ARS*) 234P

Yearbook of Critical Care Medicine, 1988, 6th Edn, Rogers, M. C., (editor), (*R*) 582